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Failure to deal with the early signs of oral squamous cell carcinoma leads to its delayed diagnosis: A case series

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Abstract

Oral squamous cell carcinoma (OSCC) corresponds to more than 90% of oral malignant neoplasms and is a global health problem. Despite the high incidence and mortality rates that demonstrate the importance of knowing the clinical aspects of this disease, as well as the vital significance of early diagnosis, OSCC is still often diagnosed tardily. Such late diagnosis is frequently due to previously misdiagnosing the lesions somehow, what unfortunately configures a reality among health professionals including dentists who practice oral clinical examinations routinely. Additional concerns relate to the difficulty of reaching trained health providers such as oral medicine specialists, particularly for the poverty-stricken population, and the patients` delay to seek treatment for early lesions, which are generally asymptomatic. It is evident that when OSCC is diagnosed early, the patient may present a better quality of life and higher survival rate; the opposite is also true for patients with late diagnosis. In that way, we aim to report a series of cases that resulted from failures in diagnosis and/or delayed diagnosis of OSCC, addressing the possible differential diagnoses and correct conduct for such cases, as well as emphasizing the importance of knowing clinical, histopathological, therapeutic and prognostic aspects of OSCC by health professionals, mainly general dentists.

Keywords

mouth neoplasms; squamous cell carcinoma; differential diagnosis; delayed diagnosis

Abbreviations

OSCC: Oral Squamous Cell Carcinoma; HE: Hematoxylin and Eosin; RAS: Recurrent Aphthous Stomatitis; TB: Tuberculosis; PCM: Paracoccidioidomycosis

Introduction

Oral squamous cell carcinoma (OSCC) corresponds to more than 90% of oral malignant neoplasms [1].This disease has high rates of incidence and mortality worldwide [2], and despite advances in prevention and treatment, it has been often diagnosed tardily [3]. The latest global estimate for the year of 2012 indicated the occurrence of 300,000 cases of oral cancer and 145,000 deaths [2]. OSCC is the sixth most common cancer among men in developing countries, and the eighth most common among women [4]. In the world, the region most affected by oral cancer is the Melanesia, with an estimated incidence of

29.1 cases per 100,000 men and 12.4 cases per 100,000 women, indicating 16.6 deaths per 100,000 men and 6.2 deaths per 100,000 women; in addition to Melanesia, Central-South Asia, Eastern, Central and Western Europe, Africa and Central America also have high rates of incidence and mortality [2]. In the United States, the estimate for the year of 2016 indicated the occurrence of 31.910 new cases of oral cancer and about 6.490 of resulting deaths [5]. Death rates have been decreasing over the past three decades; from 2006 to 2010, rates decreased by 1.2% per year in men and by 2.1% per year in women [5], and unfortunately the survival rates at 2 years, 5 years, and 10 years are 85.5%, 69.9%, and 50.2%, respectively[6]. In that way, it is evident that OSCC is one of the main public health problems worldwide [2-8].

Moreover, approximately 59.4% of patients diagnosed with OSCC have asymptomatic lesions at the onset of the disease, and the interval between diagnosis and onset of symptoms range from 3 weeks to 36 months [3,9]. This fact may explain the frequent delay in the search for a health professional, mainly by individuals from poorer socioeconomic groups, resulting in a delayed diagnosis and worse prognosis [3].

The classical clinical presentation of OSCC is an ulcer, which can be superficial, endophytic (ulcero-infiltrative) or exophytic (ulcero-vegetative); in addition to the ulcerated forms, OSCC can also appear as a leucoplasic, erythroplasic or erythroleucoplasic plaque; and when there is bone involvement, a radiographically radiolucency "in moth eaten appearance" can be observed, with irregular and non-defined borders [1].

Accordingly, such variable clinical aspects along with signs and symptoms that are not pathognomonic may lead to wide range of differential diagnoses for OSCC such as: ulcerative oral lesions of infectious diseases (syphilis, tuberculosis, leishmaniasis, histoplasmosis, paracoccidioidomycosis), traumatic lesions, periodontal disease, pyogenic granuloma, necrotizing sialometaplasia, and when intraosseous, radiolucent lesions (for instance, odontogenic tumors and cysts, osteomyelitis, and osteonecrosis), among other pathologies; hence, OSCC may be mistaken by less experienced health professionals and result in an incorrect clinical diagnosis and a consequent delayed true diagnosis that shall follow a pertinent biopsy [1,10].

The health professionals sought by patients bearing OSCC are usually head and neck specialists, general practitioners and dentists; these professionals suspect of OSCC diagnosis in 64%, 55% and 63% of cases, respectively [3].In addition, it is noteworthy that dentists are more likely to identify oral cancer at an earlier stage than doctors, once they perform routine oral clinical examinations [11]. When OSCC is diagnosed early, the patient may have a better subsequent quality of life and higher survival rates; the opposite can be applied to patients with late diagnosis [12].

Patients that present a late diagnose of OSCC tend to report greater difficulties to reach qualified health professionals [3] and also to have received some kind of medical treatment prior to the OSCC diagnosis, such as painkillers and antibiotics wrongly prescribed [12]; so, the lack of knowledge around OSCC`s aspects by some health professionals[13] urgently claims for a need to improve the oral clinical examination [14]. In that way, we aim to report a series of cases that resulted from failures in diagnosis and/or delayed diagnosis of OSCC, addressing the possible differential diagnoses and correct conduct for such cases, as well as emphasizing the importance of knowing clinical, histopathological, therapeutic and prognostic aspects of OSCC by health professionals, mainly general dentists.

Case Series Presentation

Case 1: A 61-year-old feodermic female was referred by a dentist for evaluation and diagnosis of a lesion in the floor of mouth. During anamnesis, the patient reported that the lesion had appeared 12 months before, accompanied by pain. She claimed to have looked for assistance from different health professionals; however, no professional suspected of OSCC. Previous dental appointments resulted in prescription of oral antiseptics and radiographic examinations. Also, during a neurologist consultation, anti-anxiety drugs were recommended. As previous medical history, the patient reported the presence of systemic chronic diseases: hypertension and diabetes mellitus. The patient denied having a family history of cancer and mentioned alcohol drinking and smoking habit, reporting the consumption of about 3 cigarettes a day for 35 years. During an extraoral physical exam the right submandibular lymph nodes were enlarged and painful on palpation. The intraoral exam revealed an ulcero-infiltrative lesion with elevated and hardened edges, covered by a serofibrinous pseudomembrane and located on the right side of the floor of mouth (Figure 1a). Our clinical diagnosis was OSCC and a subsequent incisional biopsy was performed a week later in a hospital after patient`s glycemic control. Microscopically, the sections stained with hematoxylin and eosin (HE) revealed an oral mucosa fragment composed of parakeratinized and hyperplastic stratified squamous epithelium, and deeper in the lamina propria, dense fibrous connective tissue surrounded sheets or islets of neoplastic epithelial cells with pleomorphic and hyperchromatic nuclei; mitoses and discrete disqueratosis, plus a mild mononuclear inflammatory infiltrate were also observed (Figure 2a). The diagnosis of OSCC grade II (moderately differentiated) was established and the patient was referred to a head and neck surgeon for evaluation. According to recently received information, the patient was submitted to oncologic treatment and presents no signs of recurrence.

Case 2: A 48-year-old melanodermic female patient was referred to us by an orthodontist for the evaluation and diagnosis of a lesion on the lateral border of the tongue. During anamnesis, the patient reported that the lesion had appeared 4 months before, with painful symptoms; and after a dentist appointment, Bismu-Jet® was prescribed (medicine composed of substances that show bacteriostatic, bactericidal and anesthetic properties and is indicated for cases of canker sores and other oral diseases). After 1 month of treatment with Bismu-Jet®, the lesion did not show favorable clinical changes, so the patient returned to the same professional, who then prescribed Kenalog in Orabase® (a synthetic corticosteroid suitable for oral inflammatory lesions and oral traumatic lesions), along with Listerine®, Cepacol® and oral rinsing with hydrogen peroxide at 3%. The patient claimed to have a family history of cancer and denied smoking or alcohol consumption. During the extraoral physical examination, cervical lymphadenopathy was not noticed, while the intraoral physical examination revealed an ulcero-infiltrative lesion with irregular surface, raised and hardened edges, measuring approximately 2 cm in length at its largest diameter and located on the left side of the tongue (Figure 1b). The diagnostic hypothesis was OSSC. An incisional biopsy was then performed under local anesthesia, and the microscopic examination revealed several islets of pleomorphic and hyperchromatic epithelial cells, along with mitoses, some disqueratosis and keratin pearls (Figure 2b) dispersed through the lamina propria and intermingled with mononuclear cell infiltration. Therefore, the histopathological diagnosis confirmed the clinical suspicion of OSCC, which was classified as grade II (moderately differentiated). The patient was referred to the head and neck surgeon for evaluation. According to recently received

information, the patient was submitted to oncologic treatment and presents no signs of recurrence.

Case 3: A 51-year-old feodermic female was referred to our Stomatology Clinic by a dentist for the evaluation and diagnosis of an oral lesion in the floor of the mouth. During anamnesis, the patient reported the appearance of the lesion 4 months before and complained about the presence of painful symptoms and mobility in the lower teeth. She also mentioned a previous dental appointment in which she was prescribed Amoxicillin (broad-spectrum antibiotic, indicated for the treatment of bacterial infections) and Nimesulide (non-steroid anti-inflammatory drug). She informed a family history of cancer and smoking habits for 36 years, (straw cigarettes). She also reported to drink distilled beverages daily. The extraoral physical examination revealed that the submandibular and submental lymph nodes were increased in volume, and also painless, fixed and hardened on palpation. The intra-oral exam revealed an ulcero-infiltrative lesion with raised and hardened edges, and located in the anterior floor of the mouth, extending to the gingival mucosa of the lower incisors (Figure 1c). The presence of black hairy tongue with limited movements was also noticed. The diagnostic hypothesis was OSCC and an incisional biopsy was performed under local anesthesia. Microscopically, dysplastic epithelial islet cells, pleomorphic and hyperchromatic, were distributed in a dense fibrous connective tissue with moderate mononuclear inflammatory infiltrate; discrete mitoses and keratin pearls were also seen after HE staining (Figure 2c); thus, the morphological aspects supported the diagnosis of OSCC. The patient was directed to the head and neck surgeon for evaluation and treatment, but unfortunately she died before starting the oncologic treatment.

Discussion

We report here three cases of OSCC affecting females, although this malignant neoplasm affects males predominantly (male-female ratio of approximately 2: 1) [15,16], most of them being smokers and drinkers [1,17]. An increasing incidence is currently observed in women, probably due to the spread of smoking habits among them [12]. In addition, the vast majority of OSCC occurs in patients over 45 years of age, which was in fact observed in this study, and the most common intraoral locations are the tongue and the floor of mouth [15,16].

The delay in OSCC diagnosis found in the cases addressed herein probably results from an unsatisfactory ability to handle such oral lesion and its respective differential diagnoses. Dentists and other related health professionals need to receive adequate training in order to avoid misdiagnoses and ineffective treatments, also referring the patient to an specialized professional or clinic immediately, and thus speeding up the correct diagnosis, as well as allowing for a consequent improved prognosis [12,18].In fact, the time interval between OSCC appearance and its effective diagnose is majorly affected by the dentists or non-specialist professionals that gain a first contact with the lesion [19].

Case 1 illustrates a late diagnosis of OSCC followed by a persistent, though ineffective clinical management of the lesion from different health professionals. In addition, case 2 addresses erroneous prescription by a dentist who assumed that the lesion was caused by bacteria, inflammation or trauma; actually, the patient was advised to use drugs that are usually prescribed for recurrent aphthous stomatitis (RAS). Nevertheless, RAS often develop on non-keratinized oral mucosa and presents as a painful round shallow ulcer with well-defined erythematous margins and yellowish-gray pseudomembranous center. In addition, RAS has a characteristic prodromal burning sensation that lasts

from 2 to 48 hours prior to the appearance of an ulcer, which may be multiple, and last approximately 10 to 14 days without scar formation [20]. In contrast, OSCC is a single and chronic lesion, usually asymptomatic at early stages [1].

Incorrect medications following an initial improper diagnosis were also prescribed in case 3. The patient was instructed to take antibiotic and anti-inflammatory drugs, as there was a suggestion of infectious or inflammatory disease instead of neoplasia. Inappropriate drug therapy has been reported to contribute to OSCC delayed diagnosis [12]. And there are in fact infectious diseases that can mimic OSCC; for instance: tuberculosis (TB) [21], histoplasmosis [22] and paracoccidioidomycosis (PCM) [23]. Nonetheless, such infections are usually associated with pulmonary symptoms, unlike OSCC [21-23].

TB is caused by *Mycobacterium tuberculosis* [24]and oral lesions are rare [21]; when TB occurs in the oral cavity, its typical presentation is a single indurated painful ulcer with irregular borders covered by inflammatory exudates [1,21,24]. Histoplasmosis, on the other hand, is caused by a dimorphic fungus called *Histoplasma capsulatum* [25] and its subsequent lesions can affect the upper aero-digestive; this lesions are commonly multiple painful ulcers and verrucous excrescences in the tongue and buccal mucosa, but can also present as deep ulcers with infiltrative edges or hard irregular nodular lesions that may be accompanied by regional lymphadenopathy [26,27].PCM is also caused by a dimorphic fungus, the *Paracoccidioides brasiliensis* [28], which is mainly found in Latin America [29]; PCM oral lesions occur simultaneously in a number of anatomical sites and are granulomatous, erythematous, and ulcerated in aspect, with hemorrhagic spotting; suchclinical manifestation is known as moriform stomatitis and can affect lips, gingiva, buccal mucosa, palate, tongue and floor of the mouth; also, there may be periodontal involvement that leads to tooth mobility [30].

Besides knowing the specific clinical features of OSCC and its differential diagnoses, the histopathological analysis is crucial for the differentiation between infectious/inflammatory lesions and malignancy [31]. Therefore, incisional biopsies are mandatory for an accurate diagnosis of conditions with similar clinical aspects [30] and should be especially performed when there is a clinical suspicion of a malignant lesion [1]. Finally, the biopsy needs to be accurately conducted to allow the pathologist to analyze not only the core of the lesion, but also its relation with the surrounding stroma and overlying epithelium; although incisional, biopsies need to strike a representative part of the lesion, and not only the necrotic center.

Conclusion

OSCC is a global health issue, and despite its high incidence and mortality rates that demonstrate the relevance of spreading public knowledge on the aspects of this disease, as well as the vital importance of an early diagnosis, this condition is still often diagnosed tardily [2-9]. The usual delay in OSCC diagnosis may relate to failures in the initial diagnosis, which may unfortunately be committed by health professionals (including dentists who perform oral clinical examinations routinely). Another important fact is that patients often procrastinate to seek treatment for initial lesions, which are generally asymptomatic. Thus, there is a need to apply measures directed to improve the way dentists and dental students learn about OSCC's epidemiology, etiology, clinical and histopathological features, treatment and prognosis. Also, public awareness of this type of cancer should increase through preventive campaigns and media dissemination. Governmental and institutional prevention programs should

"trace" and monitor high-risk individuals to oral cancer (age over 45, smokers and drinkers), in addition to encourage smoking cessation and alcohol abuse.

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Figures

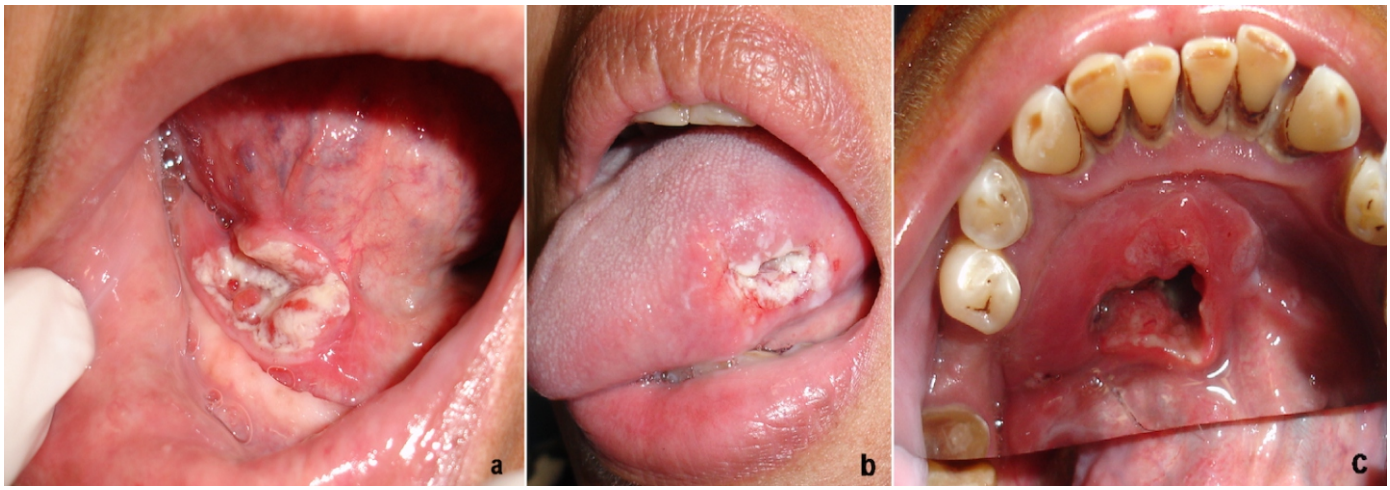

Figure 1: Clinical presentations of OSCC. (a) Case 1. (b) Case 2. (c) Case 3.

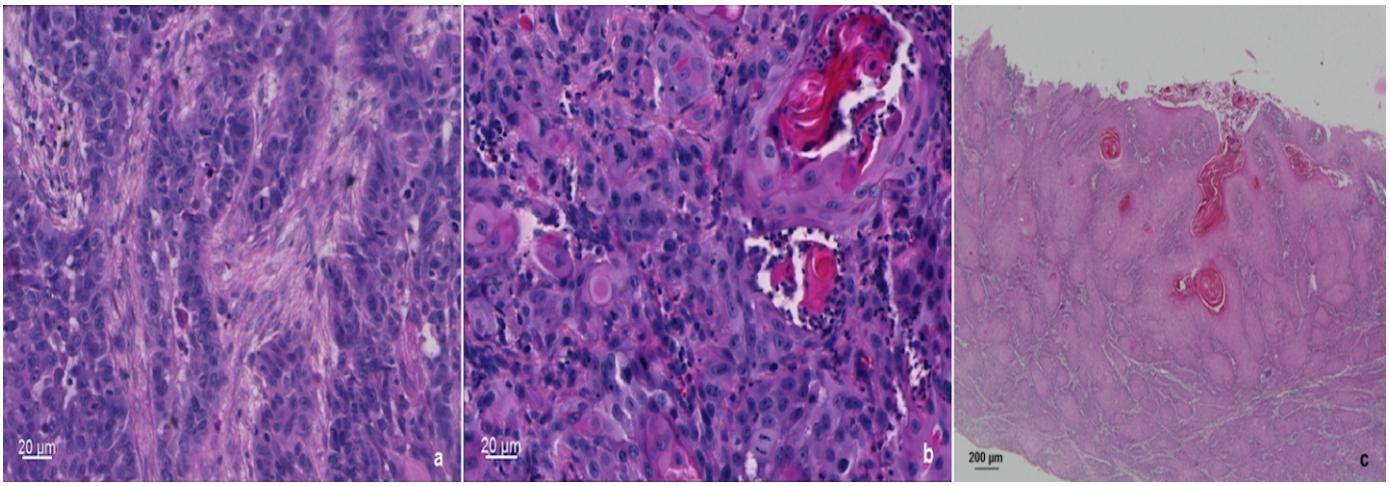

Figure 2: Hematoxylin and Eosin stains of OSCC. (a) Case 1. (b) Case 2. (c) Case 3.

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