Chapter

Oral Cancer around Dental Implants: Are the Clinical Manifestations and the Oncogenic Mechanisms Unique?

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Abstract

Osseointegrated implants have been an optimal treatment option for dental rehabilitation of fully or partially edentulous patients. Although peri-implantitis remains as the most common local risk factor for dental implant failure, the development of oral cancer involving the soft tissue around the titanium may lead to early implants loss and impact the quality of life of the patient negatively. Oral squamous cell carcinoma (OSCC) is the most common malignancy among head and neck tumors. It has higher prevalence in men over 50 years old, and in tobacco and/or alcohol users. Unfortunately, oral cancer is often detected in advanced stages, when the treatment options are limited. Thus, OSCC typically has poor prognosis. Despite the recent advances in oral carcinogenesis understanding, the relationship between dental implants and the development of malignant lesions around them is not completely understood. It has been suggested that the titanium corrosion occurring at the top of dental implants causes the release of metal ions. These ions might lead to oral epithelial genetic damage and higher susceptibility of normal mucosa to malignant transformation. The aim of this chapter was to review the clinical characteristics, diagnosis, and the possible carcinogenic mechanisms involved in oral cancer around dental implants.

Keywords: oral cancer, carcinogenesis, dental implants, titanium corrosion, delayed diagnosis

1. Introduction

Oral cancer remains as a significant cause of mortality worldwide as most of these the tumors are detected and treated in late stages. The etiology of oral cancer is multifactorial. Tobacco and alcohol are still considered the main risk factors as about 80% of the patients who develop oral tumors are tobacco and/or alcohol users [1]. Additional etiologic factors have also been suggested such as infection by human papillomavirus (HPV) and other oncogenic viruses, immunosuppression states, genetic alterations, and deficient nutrition.

Dental implants are one of the top choices for the oral rehabilitation of partially or totally edentulous patients. The stability and comfort provided by the implants-anchored crowns are among their clinical advantages. Moreover, the success rate of dental implants surpasses 94.6% [2]. However, the soft tissue and supporting structures around the dental implants remain exposed to the oral cavity and may undergo pathological changes. The most frequent lesions are those of inflammatory nature triggered by the accumulation of bacterial biofilm. When the inflammatory lesion is confined to the soft tissue, it is named as peri-implant mucositis. On the other hand, when there is loss of supporting bone, the lesion is known as peri-implantitis. Due to the high incidence of peri-implant inflammatory diseases, some dental professionals treat the lesion but do not send the specimens to the microscopical analysis. About 3.6% of the lesions are malignant tumors (mainly squamous cell carcinomas, the most common malignancy of the oral cavity) [3]. In 2001, the first cases of malignant lesions developing around dental implants were published [4–22]. Since then, the potential relationship of titanium implants with malignant tumor development has been discussed [1, 5, 13].

The aim of this chapter was to offer the readership the most recent information regarding the clinical features of oral cancer around dental implants, its differential diagnosis, and potential oncogenic mechanisms.

2. Clinical features of oral cancer around dental implants

A review of literature available until September 2021 was conducted in the PubMed/Medline database using the term "Oral squamous cell carcinoma around dental implants." Only cases with definitive microscopic diagnosis of OSCC arising in the soft tissue around one or more dental implants were included. The literature review revealed 43 cases of patients with OSCC around dental implants in the 19 published manuscripts [4–22]. All clinical and epidemiological information about the sample is summarized in the **Table 1**.

The age of patients with oral cancer around dental implants ranged from 61 to 75 years old. There was a predominance of females (24 cases - 57.14%) when compared to males (18 cases - 42.86%). The typical clinical appearance of oral cancer around dental implants was an exophytic mass (20 tumors—47.62%) with few cases presenting as ulcer (4 tumors—9.52%). The bone osteolysis was frequently observed in the area of tumor causing the implant loss in some patients. The tumors affected mainly mandible (38 cases—90.47%) of the patients with multiples osseointegrated implants. Of note, oral cancer around dental implants is frequently clinically mistaken as peri-implantitis (**Table 1**).

Although peri-implantitis is the most common local risk factor for dental implant failure, the development of oral cancer involving the soft tissue around the titanium also impact the quality of life of the patient negatively. The oral cancer can manifest as hypertrophy, erythema, and/or ulcerative lesion of the soft tissue, and these features are similar to inflammatory peri-implant diseases such as peri-implantitis and/or peri-implant mucositis, as described by others [7, 10, 11]. Furthermore, these inflammatory peri-implant diseases frequently present the same epidemiological pattern and risk factors for oral cancer, that is, patients older than 60 years old and chronic tobacco and/or alcohol consumers [1]. Although there are protocols for peri-implantitis treatment, frequently, the peri-implant tissue removed during this surgical treatment is not submitted for histopathological analysis [23, 24] Then, the number of reported cases of peri-implant malignancy seems to be low in mouth but it may be being underreported by health professionals [24]. Recently, in a study of 111 biopsies of peri-implant lesions, 3.6% of those

Author	Gender/age	Cancer site	Lesion	Risk factors*	Prev. Rep. CA	Primary diagnosis
Block et al. 2001 [4]	M/72	Mandible	Mimicked PI	Yes	Yes	PI
Shaw et al. 2004 [5]	M/67	Mandible	Exophytic mass	NA	Yes	PI
	F/69	Mandible	Mimicked PI	NA	Yes	NA
Czerninski et al. [15]	F/52	Mandible	Mimicked PI	Yes	No	PI
	M/80	Mandible	Mimicked PI	No	Yes	PI
Abu El Naaj [16]	F/70	Mandible	Exophytic white	No	Yes	NA
Schache el al. [17]	F/77	Mandible	Exophytic mass	No	No	NA
Gallego et al. [18]	F/81	Mandible	PI mass	No	Yes	OL
Kwok et al. [19]	M/71	Mandible	"Inflammatory process"	Yes	No	PI
	F/67	Mandible	Exophytic mass	Yes	Yes	NA
	M/62	Mandible	Non-healing ulcer	Yes	No	Na
De Ceulaer et al. [20]	F/77	Mandible	Mimicked PI	Yes	Yes	PI
	M/71	Mandible	Swelling	Yes	Yes	PI
	F/62	Mandible	Mimicked PI	Yes	Yes	PI
Meijer et al. [21]	F/69	Mandible	Exophytic mass	No	Yes	PI
Orhan et al. [22]	F/69	Mandible	Numb chin syndrome, with mixed RO-RL lesion	NA	Yes	NA
Pfammatter et al. [6]	F/55	Mandible	mimicked PI, numbness	Na	Yes	Metastasis
Moergel et al. [7]	F/63	Mandible	Exophytic mass	No	Yes	NA
	F/70	Mandible	Exophytic mass	Yes	Yes	NA
	M/72	Mandible	Exophytic mass	No	Yes	NA
	M/57	Mandible	mimicked PI	Yes	Yes	PI
	M/72	Mandible	Exophytic mass	NA	No	NA
	F/54	Mandible	Exophytic mass	No	NA	NA
	M/47	Mandible	Ulcer	Yes	No	NA
	M/88	Mandible	Ulcer	No	No	NA
	F/42	Mandible	Ulcer	NA	Yes	NA
	F/59	Mandible	Ulcer	NA	Yes	NA
	M/73	Maxilla	Exophytic mass	Yes	Yes	NA
	M/77	Mandible	Exophytic mass	Yes	No	NA
	F/68	Mandible	Exophytic mass	Yes	Yes	NA
	F/69	Mandible	Exophytic mass	No	Yes	NA
Marini et al. [8]	F/51	Mandible	Exophytic mass	No	No	PI
Bhandari et al. [9]	F/71	Maxilla	Erythematous	No	No	PI
Chainani-Wu et al. [10]	F/60	Maxilla	Fistula	No	No	PI
Vadim Raiser et al. [11]	F/55	Maxilla	White Exophytic mass	NA	NA	OL
	F/70	Mandible	Erythematous mass	NA	NA	NA

Author	Gender/age	Cancer site	Lesion	Risk factors*	Prev. Rep. CA	Primary diagnosis
Noguchi et al. [12]	F/65	Mandible	gingival swelling	Yes	NA	Neoplasia
Malthiéry et al. [13]	M/77	Mandible	Mimicked PI	NA	No	PI
Granados et al. [14]	M/83	Mandible	Ulcerous lesion	NA	Yes	NA
	M/60	Mandible	Verrucous lesion	NA	NA	NA
	F/54	Mandible	"Gum lesion"	NA	NA	NA
	M/64	Mandible	Excrescent lesion	NA	NA	NA

*M = Male; F = Female; Pre.Rep.CA = Previously reported cancer; PI = Peri-implantitis; OL = Oral lichen planus; NA = Not available. * Patients who smokers and/or drinkers were considered.*

Table 1.
Demographic and clinical features of patients diagnosed with oral squamous cell carcinoma around dental implants.

had histopathological diagnosis of oral squamous cell carcinomas [3]. Another investigation demonstrated that 2.9% of 68 dental implant-related lesions were oral squamous cells carcinomas [25].

Figure 1 illustrates a case report of an edentulous 64-year-old woman. She had an exophytic mass associated with ulcerated area and covered by a yellowish membrane in the anterior region of the mandible. The lesion was surrounded multiple osseointegrated implants (**Figure 1A**). She did not report adverse habits, for example, tobacco or alcohol consumption. Periapical radiographic exhibited an ill-defined bone destruction underneath the area of the lesion (**Figure 1B**). The

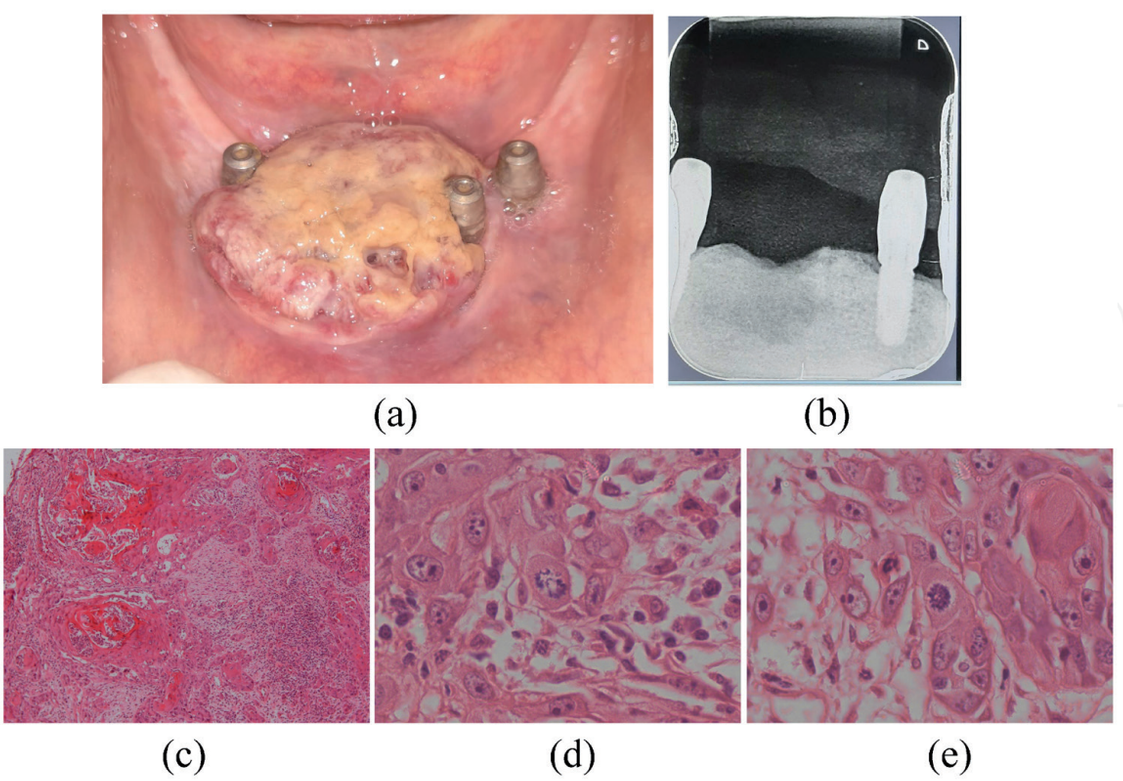

Figure 1.
Clinical and microscopic findings of oral squamous cell carcinoma around dental implants. a) Exophytic ulcer covered by necrotic tissue at the anterior-inferior alveolar ridge.b) Periapical radiograph showing an ill-defined bone loss in the peri-implant region. c) Neoplastic squamous epithelium-infiltrating subjacent submucosa with corneal pearls and discrete pleomorphism. d and e) epithelial cells with atypical mitotic figures infiltrating the tissue.

histopathological analysis exhibited keratinizing well-differentiated epithelial neoplastic cells, some undergoing atypical mitosis, and invading the subjacent fibrous connective tissue (**Figure 1C**). The diagnosis of oral cancer was confirmed.

The early diagnosis of malignant tumors around dental implants is challenging because incipient lesions may resemble inflammatory peri-implant lesions [1, 2, 4–7, 10, 12, 15–18, 21]. In the **Table 1**, 14 out of 43 cases of oral cancer surrounding dental implants (33.33%) had the primary diagnosis of peri-implant lesions. Therefore, this clinical misinterpretation might delay the diagnosis of oral cancer facilitating its dissemination and resulting in a worst prognosis of the disease. These facts underscore how critical is the histological exam of every lesion around dental implants surgically removed. Furthermore, the peri-implant lesion that does not present the classical features of an inflammatory condition and that does not respond to conventional treatment, particularly if the patient has risk factor for oral cancer, should be submitted to the biopsy and histopathological analysis [23–25].

3. Risk factors for oral cancer around dental implants

The etiology of oral cancer is multifactorial. OSCC is the most prevalent oral malignant tumor and it is associated with lifestyle risk factors such as alcohol consumption and smoking [26]. Curiously, tobacco smoking is also the predictor of dental implants failure and more smokers have post-operative infections and peri-implant crestal bone loss than nonsmokers [27, 28]. Although the information about lifestyle-related factors that predispose to oral cancer was incomplete in most of cases included in the **Table 1**, 34.88% of patients diagnosed with squamous cell carcinoma around dental implants were smokers and/or drinkers. These overlapping risk factors may drive the clinician to attribute the onset of an atypical lesion involving dental implants to a deficient or anomalous immune response of a patient who consumes tobacco and/or alcohol. However, it is essential that the clinicians are aware that the classic signs of inflammation persist in such patients and that these features are useful to distinguish a benign from a malignant lesion. Additionally, the histopathological analysis remains as the gold standard for the diagnosis of lesions located in the oral cavity [23].

A well-defined concept is that patients with previous history of cancer have higher risk of developing other tumors. Twenty-three (54.76%) of all cases of squamous cell carcinoma around dental implants arose in patients with history of cancer. Interestingly, we observed that 19 (82.60%) patients had OSCC previously. Furthermore, other patients had lung [6, 15], intestine [15], thyroid [17], and breast [17, 22] cancer previously. As the development of OSCC has been also associated with genomic instability and genetic predisposition [1], one can hypothesize that a patient who had a malignant lesion are more susceptible to local aggressions such as the contact of the soft tissue with dental implant materials.

4. Carcinogenic mechanisms associated with osseointegrated dental implants

Titanium is one of the most common components in implants alloys used in dental and medical fields [1, 29]. High biocompatibility, appropriate mechanical properties, inertness, and corrosion resistance are among the main advantages of titanium [25, 29, 30]. When the titanium implant is installed in extra oral sites, where it is protected from the contact with the environment, it has inert behavior. On the other hand, dental implants are continuously exposed to the oral cavity hostile conditions [31]. The area between the implants and the abutment

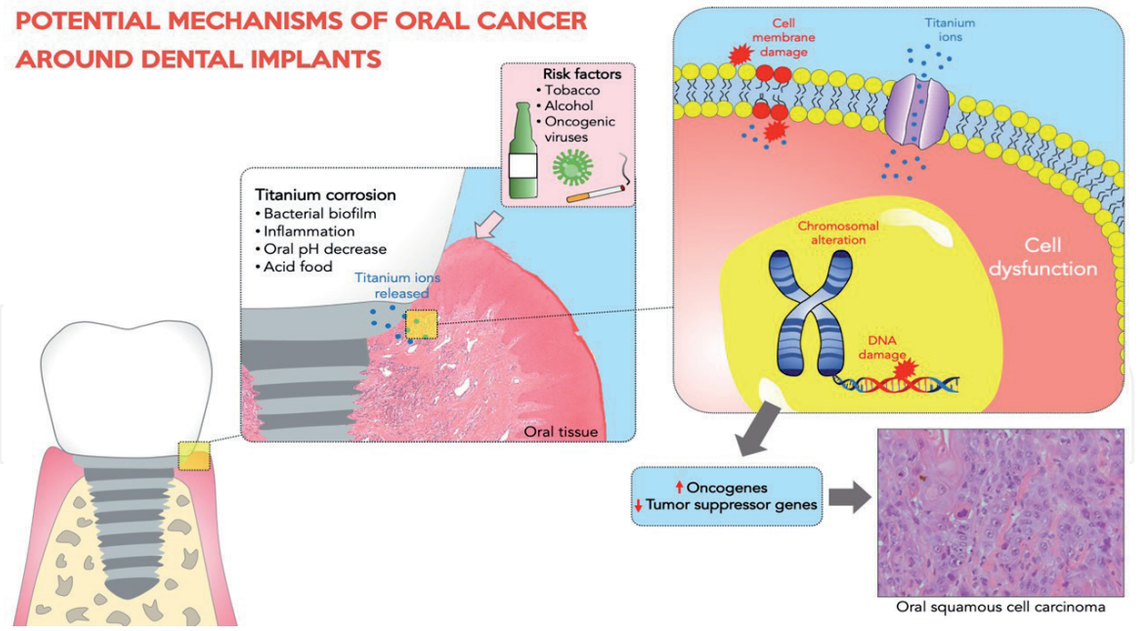

Figure 2.
Illustration of potential risk factors and mechanisms on the development of squamous cell carcinoma around dental implants.

or the prosthetic crown is particularly susceptible to the bacterial biofilm accumulation, saliva, pH and temperature changes, and functional micromotion (**Figure 2**) [31].

When the dental implant surface is exposed to any source of oxygen or nitrogen, a chemical reaction takes place and a thin layer of titanium dioxide (TiO_2) is formed and deposited in the outer surface of the implants. This layer is extremely resistant to corrosion. However the chemical agents of the oral cavity can reduce the protection of the dioxide deposit and induce the corrosion development [31]. Saliva and other chemicals introduced into the oral cavity through feeding or in contact with bacterial biofilms influence the gradual biodegradation of metallic structures including the titanium used in dental implants [29]. Furthermore, acidic solution combined with mechanical friction strength potentiates the damages to the implants surfaces. Interestingly, some studies with cytology have demonstrated the presence of titanium particles in the peri-implant tissues [23, 25] regardless of the presence of peri-implantitis or peri-implant mucositis. It has been suggested that this material accumulation may be the result of the corrosive process of the dental implants [29, 30, 32], implant-abutment friction at the installation of the implants, and/or implantoplasty [29, 31, 33, 34]. The degree of titanium corrosion can be influenced by quality and quantity of saliva, diet, alloy polishing, genetics, oral hygiene, amount and distribution of the occlusal forces, and microbiota [29, 30, 32].

The above data show that titanium is not entirely bioinert as suggested years ago. Then, even with their good biological properties, titanium alloys are susceptible to corrosion attack with release of metal ions to the surrounding hard and soft oral tissues, lymph nodes, peripheral, and even distant organs [30]. Consequently, titanium ions have been implicated in the development of oral cancer around dental implants [1, 34].

As stated previously, the relationship between titanium dental implants and oral cancer has been suggested based on the increasing number of tumors arising in the peri-implant tissue. However, as far as we know, there is not any study dedicated to unveil the potential carcinogenic mechanisms triggered by titanium ions.

Titanium particles have been shown to induce the expression of breast cancer gene 1 (BRCA1) and checkpoint kinase 2 (CHK2) in epithelial cells *in vitro* [35]. These proteins are markers of DNA damage response. Additionally, titanium also triggered the generation of reactive oxygen species (ROS) [36, 37]. The chronic exposure of the epithelial cells to aggressive factors may increase the probability of mutations that might not be detected by the immune system. Indeed, the chronic inflammatory response seems to be also modulated by titanium, especially when there is accumulation of bacterial biofilm. Higher amounts of titanium ions in peri-implant soft tissue with inflammatory process are observed when compared to healthy tissues [25, 38]. Accordingly, titanium nanoparticles induced stronger pro-inflammatory response in macrophages regardless of the association with lipopolysaccharide from *Porphyromonas gingivalis* [40] and by increasing the secretion of interleukin (IL)-6, IL-1β, and tumor necrosis factor-alpha (TNF-α) by macrophages *in vitro* [38, 40]. Taken together, all these disturbances in the peri-implant micro-envinoment may persist for years and, gradually, predispose the epithelial cells to sequential mutations until the malignant state is reached.

In 2006, the International Agency for Research on Cancer (IARC) classified the titanium dioxide as a possible carcinogen for humans [41]. However, in view of the few case reports of oral cancer around dental implants the authors were unable to exclude the existence of other confounding carcinogens as tobacco and/or alcohol [1, 7, 19].

5. Conclusion

The literature review showed that most cases of OSCC around dental implants had initial clinical features compatible with peri-implantitis. Therefore, this clinical misinterpretation of an inflammatory process in peri-implant mucosa may delay the diagnosis of oral cancer facilitating the local progression and dissemination of cancer cells, resulting in worst patient's prognosis. Thus, the peri-implant lesion not responding to conventional anti-inflammatory treatment, particularly if the patient has risk factor for oral cancer, should be submitted to the biopsy and histopathological analysis, avoiding delay in the diagnosis of the tumor.

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Conflict of interest

The authors declare they do not have conflict of interest.

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