



Clinicopathologic evaluation of malignancy adjacent to dental implants

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Objective. The aim of this study was to describe a new case series of peri-implant malignancy, review the literature, and discuss the implications of malignancies resembling peri-implantitis.

Study Design. This study was a retrospective analysis of cases from 2000 to 2016.

Results. Seven patients (two males and five females), aged 44 to 89 years, were included, representing 1.5% of oral malignancy cases. Five cases were squamous carcinoma, one of basal cell carcinoma, and one of carcinoma of metastatic origin. Six cases presented with nonulcerated overgrowth, with bone loss in three and massive osteolysis in one. Misinterpretation as peri-implantitis delayed diagnosis in six cases. Risk factors included previous oral malignancy (2), potentially malignant conditions (2), and smoking (1). Of the 47 cases in the English language literature, 85% were squamous cell carcinoma and 8.5% had distant metastasis. Most cases had one or more risk factors.

Conclusions. Peri-implant malignancy may represent up to 1.5% of oral malignancy cases. Clinical features imitating peri-implantitis may delay diagnosis. Lesions failing to respond to treatment, especially in patients with pre-existing risk factors, should significantly increase suspicion. Histopathology is crucial for diagnosis. (Oral Surg Oral Med Oral Pathol Oral Radiol 2017;123:103-112)

Peri-implantitis (PI) is a common disease involving the mucosa and alveolar bone surrounding dental implants. The clinical presentation includes erythema, swelling, suppuration, pocket formation, and bone loss.¹ It is considered a multifactorial condition, attributed to bacterial infections, poor oral hygiene, surgical trauma, genetic predisposition, implant surface characteristics, faulty or incorrect prosthetic design, occlusal overload, or improper surgical placement. There are no universally accepted protocols for the treatment of PI. In the majority of cases, peri-implant tissue removed during treatment is not submitted for histopathologic examination. Thus, there is only sparse information in the literature regarding the microscopic findings in PI. A review of several small case series, which included analyses of biopsy material from PI, reported hyperplasia and ulceration of pocket epithelium and the presence of a mixed population of inflammatory cells.² A study of 117 biopsies from PI cases reported that close to 50% of cases did not exhibit simple inflammatory changes. Instead, other potentially aggressive lesions, such as pyogenic granuloma, giant cell granuloma, or *Actinomyces*-related inflammation were diagnosed.³ These entities exhibit clinical and radiographic characteristics that imitate PI but fail to respond to conventional treatment modalities. Rarely, primary as well as

metastatic tumors have been described around or adjacent to dental implants, some of which also clinically imitate PI.⁴⁻²⁹

The objectives of the present study were to describe a new case series of malignancy around dental implants, investigate the spectrum of clinicopathologic characteristics, and discuss the implications of clinical features overlapping with those of conventional PI.

Guiding the present study were two propositions: (1) Malignancy in conjunction with dental implants may not be as rare as previously believed and is possibly underdiagnosed because it imitates PI; (2) patients presenting with malignancies in conjunction with dental implants may have recognizable predisposing factors for oral cancer unrelated to the dental implant procedure.

MATERIALS AND METHODS

We performed a retrospective clinicopathologic analysis of all cases diagnosed with implant-related malignancy collected from our archives between 2000 and 2016. Data collected from patients' files and pathology reports included age, gender, location of the tumor,

Statement of Clinical Relevance

Clinicoradiographic presentation of peri-implant malignancy may mimic peri-implantitis and lead to delayed diagnosis. Peri-implant malignancy most frequently occurs in patients with recognized risk factors for oral cancer. Increased awareness of the possibility of primary or metastatic malignancy imitating peri-implantitis and biopsy are recommended in patients at risk.

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clinical presentation, duration between the first report of signs and symptoms and actual diagnosis of cancer, risk factors or predisposing factors, treatment, and follow-up.

Literature review (using PubMed and Google Scholar) was performed on data published between 2000 and 2016 in English (or with an abstract in English). All types of articles, including reviews and case reports, were retrieved. The key words included “gingiva,” “mandible,” “maxilla,” “dental implant,” “cancer,” “malignant,” and “malignancy”; both human and animal studies were retrieved. The information of interest included age, gender, location of the tumor, clinical presentation, duration between the first report of signs and symptoms and actual diagnosis of cancer, risk factors or predisposing factors, treatment, and follow-up.

The present study was written in accordance with the ethical requirements (both Israeli and Good Clinical Practice/Pharmaceuticals for Human Use standards) for clinical trials.

RESULTS

Literature review

A search of the literature published between 2000 and 2016 yielded 25 articles, describing 47 cases of oral malignancy involving dental implants.⁴⁻²⁹ We noticed a sharp increase in the number of reported cases in the last 10 years (Table I).

Cases in the literature showed a female predominance, with a male/female ratio of 1:1.5. The mean age of patients was 67.2 years. The mandible was involved in 42 cases (89.4%) and the maxilla in five cases (10.6%). Forty cases (85.1%) were squamous cell carcinoma (SCC), four (8.5%) were metastatic spread from lung or breast cancer, and one case each (2.1%) were osteosarcoma, plasmacytoma, and lymphoma. Peri-implant malignancies were primary tumors in 29 cases (61.7%), recurrent or second primary in 11 cases (23.4%), and metastasis from distant tumors in 4 cases (8.5%). Recognized risk factors for oral cancer included potentially malignant conditions (erythroplakia, leukoplakia, oral lichen planus [OLP] or proliferative verrucous leukoplakia [PVL]) in 21 cases (44.7%). Previous oral malignancy was reported in 22 cases (46.8%), primary extra-oral malignancy in eight cases (17%), past or present smoking in 15 cases (31.9%), and alcohol abuse in eight cases (17%), with co-existing risk factors in several cases. Detailed information on history of smoking (e.g., pack-years) was not given in the majority of cases. Information on alcohol use (or abuse) was also unsatisfactory; in most cases, it was only mentioned as a potential risk factor, without any quantitative information.

The initial clinical appearance imitated PI in 17 cases (36.2%) and presented as a mass or swelling in 18 cases

(38.3%) and as an ulcer or ulcerated mass in nine cases (19.1%). In one case (2.1%), numb chin syndrome as a metastatic lesion was described.

New cases

The study included seven patients, two males and five females (M:F = 1:2.5). The age range was 44 to 89 years (mean 69 years). The number of cases of oral malignancy (primary tumors and metastases from extraoral sites) in the archives of pathology was found to range between 30 and 35 new cases per year during the period 2000-2016. Peri-implant malignancy was thus calculated to represent between 1% and 1.5 % of all oral malignancies.

In five cases (71.4%), the diagnosis was SCC (Figures 1 and 2); in the remaining cases, one case (14.3%) each was of basal cell carcinoma (BCC) (Figure 3) and metastatic carcinoma, most probably from the lungs (Figures 4A and 4B). Five cases (71.4%) occurred in the mandibular alveolar mucosa and two cases (28.6%) in the maxillary alveolar mucosa (Table II).

Clinical presentation was variable and included erythematous nonulcerated overgrowth in six cases (85.7%) and ulcerated erythematous mass in one (14.3%). Peri-implant bone loss was documented in three cases (47.8%) and massive osteolysis with expansion in one (14.3%).

Predisposing or risk factors were identified in five cases. Case 1 had a diagnosis of lower lip BCC of cutaneous origin, extending onto the mandibular alveolar mucosa, 3 years before implantation. A first local recurrence was resected 2 years after the diagnosis. One year after implantation, an overgrowth around a mandibular implant was removed and a biopsy performed, resulting in the diagnosis of BCC. It was considered a recurrence by extension from the original tumor because of the tumor's proximity to the margin of the previous resection. The patient had not received radiation therapy. Case 2 was a heavy smoker for approximately 40 years; case 4 had linear white lesions on the adjacent buccal mucosa, clinically suspicious for OLP or leukoplakia (no biopsy was performed before the discovery of the malignancy); case 6 presented a red-white lesion on the buccal mucosa, which was clinically consistent with OLP or erythroleukoplakia, (no biopsy was performed before the discovery of the malignancy); case 7 had been diagnosed with PVL that had been present for 6 years, during which time the patient presented with two existing SCC lesions in two different locations, 4 years and 1 year before peri-implant involvement. She had been treated by surgery alone for the first tumor of the right buccal mucosa, developed a peri-implant malignancy approximately 4 year later on the left buccal mucosa and mandibular

Table I. Chronologic summary of cases, 2000-2016

Source	M/F, age	Location	Risk factors	Clinical presentation	Diagnosis
Block et al., 2001 ⁴	M, 72	Mand. gingiva and bone	VC three times, leukoplakia, past smoking	Mimicked PI	SCC
Shaw et al., 2004 ⁵	M, 69	Mand. gingiva and bone	Previous SCC	Mimicked PI, pathologic fracture	Rec. SCC
	F, 69	Mand. gingiva and bone	Previous VC, leukoplakia, SCC	Mimicked PI	Rec. SCC
Czerninski et al., 2006 ⁶	F	Mand. gingiva and bone	OLP, smoking	Mimicked PI	Primary SCC
	M	Mand. gingiva and bone	Previous colon and oral cancer	Mimicked PI	Rec. SCC
Verhoeven et al., 2007 ⁸	F, 67	Mand. gingiva and bone	Lung cancer	Mimicked PI	Metastasis from lung cancer
Dib et al., 2007 ¹⁰	F, NA	Mand. gingiva	Breast adenocarcinoma	Swelling and pain	Metastasis from breast cancer
Abu El Naaj, 2007 ⁷	F, 70	Mand. gingiva and bone	Thyroid and breast cancer	Exophytic white lesion, bone loss	SCC
Abu el Naaj, 2007 ⁷	M, 72	Mand. gingiva and bone	OLP, smoking	Ulcerated mass	SCC
	F, 75	Mand. gingiva and bone	Solitary plasmacytoma spine	Peri-implant mass, bleeding, bone loss	Solitary plasmacytoma
Schache et al., 2008 ¹⁵	M, 77	Mand. gingiva and bone	None	Peri-implant mass, discomfort, bony erosion	SCC
Gallego et al., 2008 ¹²	F, 81	Mand. gingiva and bone	OLP and previous SCC	Peri-implant mass	Rec. SCC
Kwok et al., 2008 ¹³	M, 71	Mand. gingiva	Past smoking, alcohol	“Inflammatory process”	SCC
Kwok et al., 2008 ¹³	F, 67	Mand. gingiva	Previous tongue SCC (×2), breast cancer, past smoking, alcohol	Exophytic mass, “granulation tissue”	Second primary SCC
Kwok et al., 2008 ¹³	M, 62	Mand. gingiva	Alcohol and tobacco.	Nonhealing ulcer	SCC
McGuff et al., 2008 ¹⁴	F, 38	Max. gingiva	None	Mass	Osteosarcoma
Eguia del Valle et al., 2008 ¹¹	M, 76	Mand. gingiva and bone	None	White exophytic mass, ulcer, bone loss	SCC
Gallego et al., 2009 ¹⁶	F, 70	Mand. gingiva	None	Ulcer and pain, related to cantilever	SCC
Gulati et al., 2009 ¹⁷	F, 62	Mand. gingiva and bone	Previous SCC, smoking	Mimicked PI	Rec. SCC
De Ceulaer et al., 2010 ¹⁸	F, 77	Mand. gingiva and bone	Previous SCC	Mimicked PI	Rec. SCC
De Ceulaer et al., 2010 ¹⁸	M, 71	Mand. gingiva	Previous SCC	Mucosal nonulcerated swelling	Rec. SCC
De Ceulaer et al., 2010 ¹⁸	F, 62	Mand. gingiva and bone	Previous SCC	Mimicked PI	Rec. SCC
Meijer et al., 2010 ¹⁹	F, 69	Mand. gingiva and floor of mouth	Previous SCC	Exophytic mass	SCC
Orhan et al., 2011 ²⁰	F, 69	Mand., bone	Breast cancer	Numb chin syndrome, with mixed RO-RL lesion	Metastasis from breast cancer
Pfammatter et al., 2012 ²⁴	F, 55	Mand. gingiva and bone	Pancreatic cancer, NSCLC	Initial presentation mimicked PI; later developed numbness	Metastasis NSCLC
Bhatavadekar, 2012 ²²	M, 54	Max. gingiva	None	Swelling and ulcer,	SCC
Marini, 2013 ²⁶	F, 55	Mand. gingiva and bone	OLP, long-term steroid use	Mimicked PI	SCC
Moergel et al., 2014 ²⁵	15 cases	14 mandible	9 previous SCC	10 exophytic mass	SCC
	F/M 8:7	1 maxilla	10 leukoplakia 2 erythroplakia 3 OLP	4 nonhealing ulcer 1 mimicked PI	
Nariai, 2016 ²⁸	F, 67	Mand. gingiva and bone	Previous SCC	Mimicked PI	SCC
Bhandari et al., 2016 ²⁷	F, 71	Max. gingiva and bone	None	Mimicked PI	SCC
Raiser et al., 2016 ²⁹	M, 72	Maxilla	None	Nonulcerated mass	B-cell lymphoma
	F, 55	Mandible	OLP	Gingival overgrowth	SCC
	F, 70	Mandible	OLP	Nonulcerated mass	SCC
		All 3 gingiva and bone			

Mand., mandible; Max., maxilla; NSCLC, non-small cell lung cancer; OLP, oral lichen planus; PI, peri-implantitis; Pot. Malignant, potentially malignant lesions; Rec, recurrent; RO-RL, radiopaque-radiolucent; SCC, squamous cell carcinoma; VC, verrucous carcinoma.

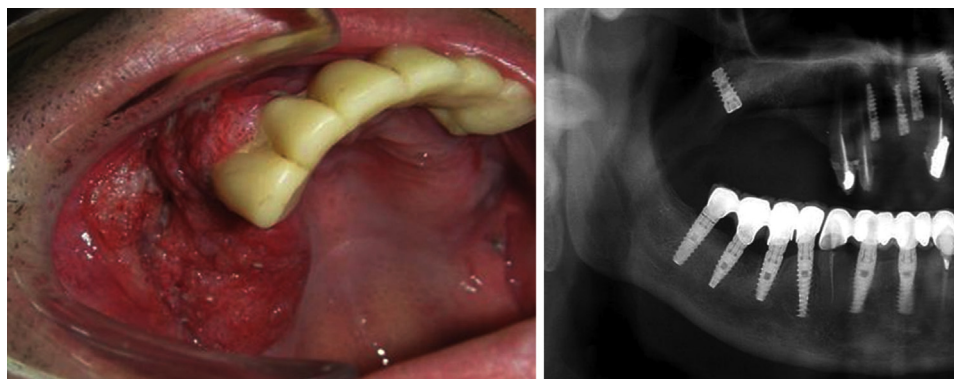


Fig. 1. Squamous cell carcinoma of right posterior maxillary gingiva, 8 months after initially being interpreted as “disturbed healing” of implantation site (case 5).

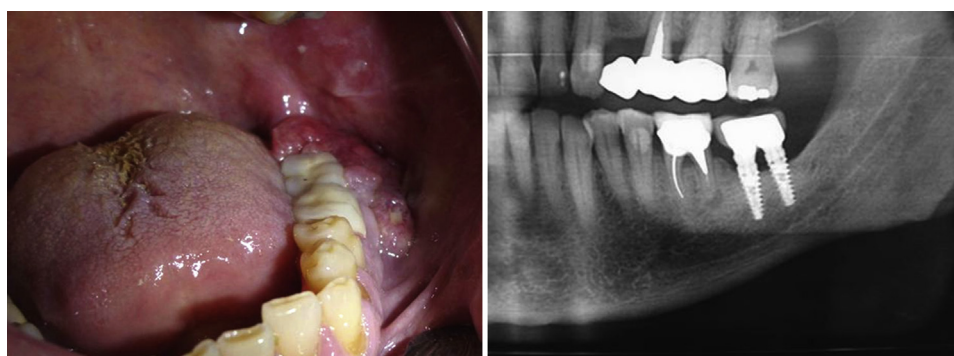


Fig. 2. Peri-implant: Squamous cell carcinoma, posterior left alveolar mucosa (right panel), with minimal bone loss (left panel). The adjacent buccal mucosa exhibits white linear lesions clinically suspicious for lichen planus or leukoplakia (case 4).

alveolar mucosa, and was treated by surgery and radiotherapy. The implant was inserted about 1 year before the peri-implant tumor had been recognized. Thus, there were two cases with a previous oral mucosal malignancy, two cases with suspected potentially malignant conditions (OLP/erythroleukoplakia), and one case with a long history of heavy smoking. Only two cases had no identifiable high-risk habits or predisposing factors for oral cancer.

In six cases (85.7%) for which information on duration was available, there was a delay of up to 8 months before a biopsy was performed, during which time conventional treatment for PI or no treatment was performed because the initial signs and symptoms were misinterpreted as PI. The time span between the implantation and the first sign of malignancy varied significantly, ranging from several months (cases 4, 5, and 6) to 1 year (cases 1) and 13 years (case 2). The study was conducted in a tertiary referral center; thus, for most cases, detailed implant-related information was not available (e.g., brand, geometry, surface characteristics).

The choice of prosthetic reconstruction was overdenture in two cases (cases 1 and 7) and porcelain

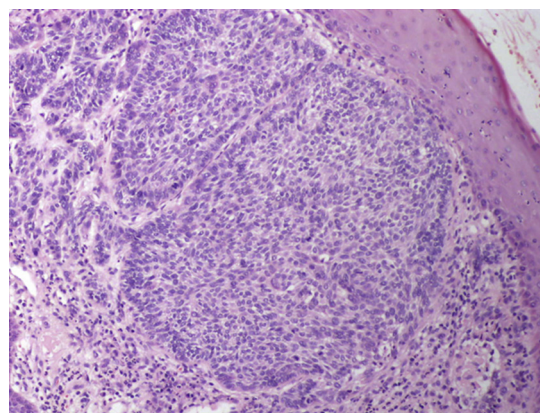


Fig. 3. Basal cell carcinoma presenting as peri-implant mass, anterior mandibular alveolar mucosa. (Hematoxylin and eosin, original magnification $\times 200$) (case 1).

fused to metal crowns in five cases (cases 2-5). Treatment modalities included surgery, radiotherapy, chemotherapy, or a combination of these (see Table II). Of the seven patients, four (57.1%) were free of disease 1.5 to 2 years after treatment, one was alive with disease at the 6-month follow-up, and one died as a

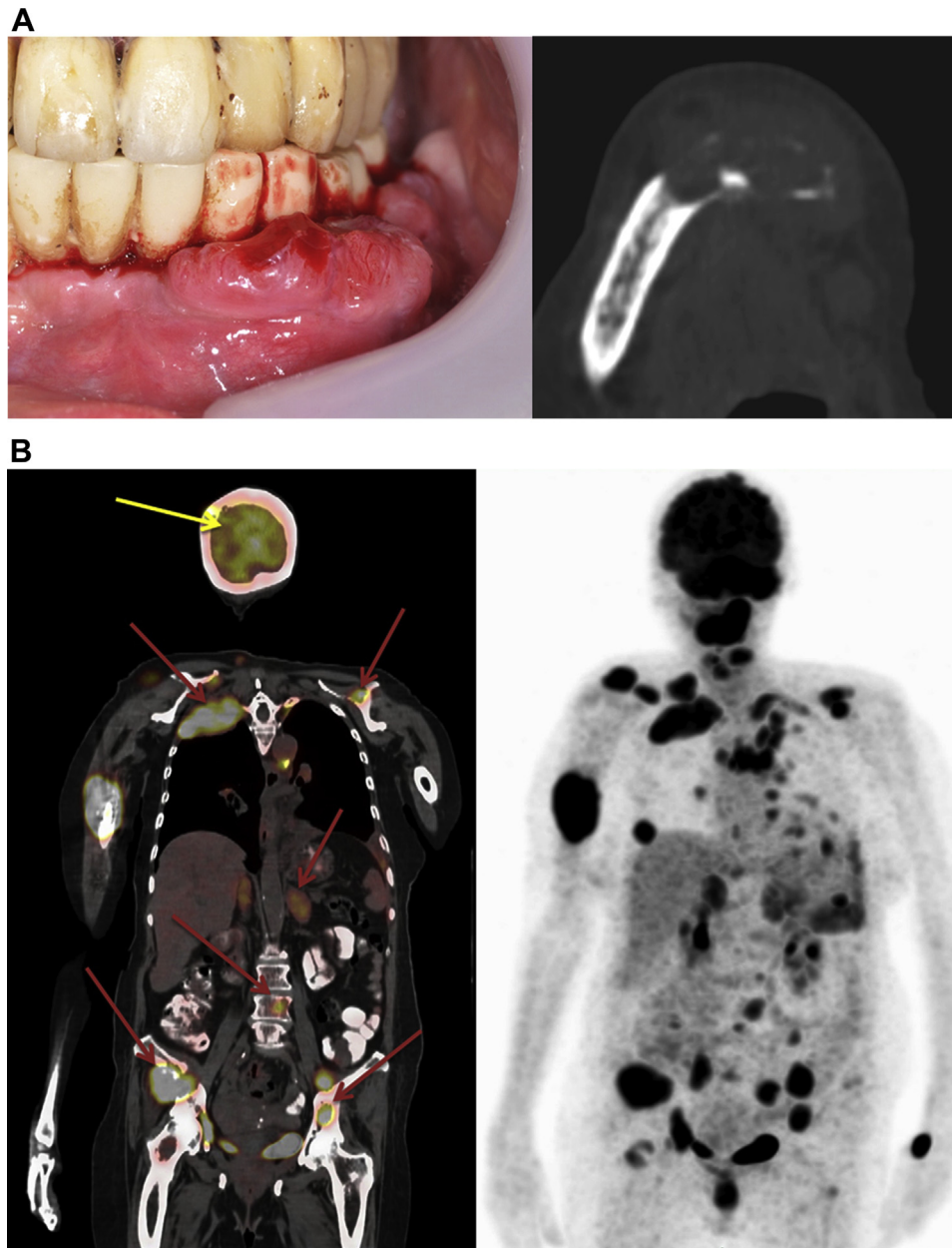


Fig. 4. **A**, Easily bleeding gingival overgrowth, involving left mandibular implants (*right panel*). Computed tomography (CT) scan revealed massive osteolysis and compromised cortical integrity. (Cropped image from CT scan, horizontal plane, level of body of mandible) (case 2). **B**, Bone scan and positron emission tomography—CT (PET-CT) demonstrated multiple hot spots, including brain, right lung, ribs, adrenals, vertebrae, scapula, arm, and pelvis. The lung tumor was the primary tumor, with multiple metastatic deposits, including in the mandible in the area adjacent to dental implants (case 2).

result of undetermined causes immediately after completion of radiochemotherapy. The patient with metastasis from the lung died as a result of disease within 5 months of diagnosis.

DISCUSSION

The global number of reported cases of peri-implant malignancy cases is low and suggests an extremely low incidence. This concept would be correct if one

assumed that the global number of reported cases reflects actual incidence. However, we could not find epidemiologic data regarding implant-related malignancy. The fact that in the present study, seven new cases were collected from one medical center in Israel, a country with a population of approximately eight million, compared with only 47 cases ever reported in the world literature (seven of which also originated in Israel),^{6,7,29} indicates that the actual incidence may be

Table II. Summary of clinical and histopathologic data of new cases

No	M/F, age	Location	Diagnosis	Clinical presentation	Predisposing factors/risk factors	Duration before diagnosis	Treatment	FU
1	F, 89	Ant. Mand. gingiva	BCC	Friable mass, bleeding	BCC of lower lip with BCC of mand. ridge	NA	Local excision only	Died of unrelated causes, 1 year
2	F, 70	Post. Mand. gingiva and bone	Metastasis, M/P lung Multiple metastases	Gingival overgrowth, expansion, bleeding, bone loss, pain, paresthesia, trismus	Heavy cigarette smoking	1 month	Palliative	DOD 5 months
3	F, 73	Premolar max. gingiva and bone	SCC	Ulcerated mass, pain 3 months before diagnosis SCC cervical LN	None	3 months	Part. maxillectomy, ND, Radiotherapy	Died after chemo radiotherapy. Cause unknown
4	M, 71	Post. mand gingiva and bone	SCC	Erythematous granular mass, bone loss	Suspected OLP/leukoplakia	5 months	Marg. Mandibulectomy, chemoradiotherapy, recurred after 2 months	Lost for FU
5	M, 44	Post. max. gingiva	SCC	Erythematous granular mass, Disturbed healing following augmentation and implants	None	8 months	Part. maxillectomy, ND chemoradiotherapy	FOD, 2 years
6	F, 59	Post. mand. gingiva and bone	SCC	Erythematous granular mass, pain, bone loss	Probably lichen planus	Several months	Mandibulectomy, ND, radiotherapy	FOD 18 months
7	F, 77	Mand. premolar gingiva	SCC	Peri-implant mass, removed with laser treatment, recurred after few weeks	PVL 2 previous oral SCC	Several months	Marginal mandibulectomy	Recurrence in 4 months, AWD 1 year

Ant., anterior; *AWD*, alive with disease; *BCC*, basal cell carcinoma; *DOD*, dead of disease; *FOD*, free of disease; *FU*, follow-up; *LN*, lymph node; *MP*, most probably; *Mand.*, mandible; *Marg.*, marginal; *Max.*, maxilla; *ND*, neck dissection; *OLP*, oral lichen planus; *Part.*, partial; *Post.*, posterior; *PVL*, proliferative verrucous leukoplakia; *SCC*, squamous cell carcinoma.

much higher than currently reported. In the present series, peri-implant malignancy comprised up to 1.5% of all new cases of oral malignancy (including metastases from extraoral sites), which indicates that it may not be all that rare. These facts suggest that the low number of such cases reported in the literature results not from this entity being genuinely rare, but rather from underreporting.

Two previous articles addressed the question of the incidence of cancer around implants. Based on the assumption that nine million implants were implanted in the United States in a 10-year period and 20 cases of peri-implant cancer were reported, the theoretical standardized incidence ratio was calculated to be 0.00017/million/year.²² This is a very low figure in comparison with cancer related to background radiation, for example, for which the calculated standardized incidence ratio was 20/million/year. A recent study has provided more concrete information: 10,986 implantations were performed over a 16-year period (1995-2011), of which 297 were performed in patients with oral SCC; in these patients, dental implants were inserted during remission after ablative surgery. A total of 15 cases of peri-implant SCC were recorded during this period, 3% among patients with previous oral SCC and 0.056% in the remaining 10,689 implantation cases.²⁴ It is obvious from these data that the incidence in patients with a previous oral malignancy is significantly higher and is very low in those outside this risk group. However, from many studies on oral cancer, the risk of recurrence in patients with a previous oral SCC was reported to reach a global figure of 23%,³⁰ 27% to 100% in T4 tumors.³¹ In comparison, a 3% rate of peri-implant recurrence seems to rule out any specific preferential occurrence of cancer in a peri-implant location. Thus, so far, there is no epidemiologic evidence to support any specific risk for cancer associated with dental implants, and this should therefore have no influence on surgical considerations.

Analysis of the characteristic features of peri-implant malignancy from the literature and from our new case series highlighted numerous similarities; there seems to be a female predominance, in contrast to a general male predominance in oral cancer incidence, and a clear predilection for the mandibular mucosa. The majority of patients in both groups had one or more recognized predisposing factors for oral cancer, such as potentially malignant conditions, previous oral malignancy, or a history of primary extraoral malignancy that may subsequently metastasize to the oral mucosa or the jaws. OLP is a premalignant condition, which, in most cases, exhibits multifocal involvement. It has been reported to undergo dynamic changes in size, extent, and clinical appearance over time.³² Thus, the entire oral mucosa

should be considered as at risk for malignant transformation, not only areas with active lesions of OLP when malignancy is diagnosed. Leukoplakia and erythroleukoplakia are also considered to be predisposing factors for oral cancer, and both may be multifocal as well. In the present cases, the mucosal changes suggesting OLP or leukoplakia were only noticed while analyzing the clinical picture. As no biopsy had been performed before the diagnosis of SCC, the specific predisposition for oral cancer is only a suggestion based on the clinical image. PVL is also a multifocal disease, considered to carry a high risk of malignancy at any oral site.³³ Smoking and alcohol abuse have also been reported in some cases, although information on these lifestyle factors was incomplete in most cases. The majority of peri-implant malignancy occurred within these at-risk populations.

The majority of cases of malignancy in conjunction with dental implants in both the literature and the present series have been of SCC, and most were primary tumors, which is in agreement with the distribution of cancer types in oral cancer in general. However, cases of BCC mimicking PI have not been described previously. In the case of BCC in the present series, there was no question regarding its extraoral origin, since the primary tumor was described to involve skin and extend onto the oral and alveolar mucosae when it first recurred. The peri-implant lesion was a second recurrence at the margin of the primary resection, unique only in the fact that it presented intraorally with features mimicking PI. Primary oral BCC is very rare, and its existence is not universally accepted. Only one case involving the gingival mucosa has been found in the literature³⁴; however, the present case is clearly not one of primary oral BCC.

Peri-implant metastatic deposition from distant extraoral tumors (breast or lung) have been described in the literature and were also observed in the present series, representing the second most frequent implant-related malignancy after SCC.^{10,20} Metastases to the oral mucosa and jaws from extraoral malignancy are not uncommon and have been reported to be most frequently found in the gingiva, with an apparent predisposition for the posterior mandibular gingiva.²¹ Characteristics of metastases from extraoral sites associated with dental implants fall within those described for metastases to the oral mucosa and jaws. There is now concrete evidence that the spectrum of malignancies arising as peri-implant lesions is wider than had been previously appreciated. In addition to SCC, metastases from extraoral tumors, as well as lymphoma, osteosarcoma, and BCC, may be encountered on rare occasions.

There is very little information to suggest any pathways that would link dental implants and cancer. In

relation to orthopedic stainless steel plates, an annual increase of 0.12% a year for osteosarcoma has been reported and is suggested to be a result of corrosion caused by surface imperfections and chronic inflammation.³⁵ No such data exist regarding titanium dental implants. Only a single in vitro experiment showed that exposure to titanium particles demonstrated a dose-responsive induction of chromosomal instability in human fibroblasts, similar to that induced by heavy metal and low-dose radiation exposure.³⁶ Although titanium corrosion is a recognized phenomenon in dental implants, its clinical relevance remains poorly understood. There are conflicting results in the literature, with no clear evidence that corrosion material (as opposed to titanium-oxide nanoparticles) can play a role in carcinogenesis.³⁷⁻³⁹

In recent years, a correlation between chronic inflammation and malignant transformation has been established for various types of cancer, such as colon cancer in patients with Crohn disease, esophageal cancer in patients with Barrett esophagitis, and many others.^{40,41} It has been suggested that unresolved inflammation can continue to perturb the cellular microenvironment and lead to alterations in cancer-related genes and posttranslational modification in the proteins involved in the cell cycle, DNA repair, and apoptosis.⁴² Because PI is a chronic and prolonged inflammatory condition, this may theoretically provide a pathway for malignant transformation; however, there is no concrete evidence, as yet, for this in relation to implants in the existing literature.

There is wide variation in the time span reported between implantation and diagnosis of peri-implant malignancy, ranging from several months to as much as 13 years, as seen in the present series; thus, it is not possible to identify a particular correlation with time. Regarding the period between a primary oral SCC and a peri-implant secondary lesion, there are also wide variations, ranging from several months to several years.

In the absence of a proven risk for peri-implant malignancy, one principal point needs to be emphasized: When malignancy does occur in spatial relationship to existing dental implants, the initial similarity to the clinical presentation of PI is a diagnostic trap. Clinical features initially imitating PI were evident in both implant-associated SCC and in cases of metastasis from extraoral sites or single cases, such as BCC, lymphoma, or osteosarcoma.

In the majority of patients receiving dental implants and undergoing prosthetic rehabilitation, the dentists who are their primary caregivers may have little or no experience with oral cancer. These dentists tend to interpret the initial signs and symptoms as consistent with PI, the more common and well-recognized phenomenon. Malignancy may not be suspected until the

lesions have progressed significantly. Biopsy is not yet an integral part of the management of PI, and even when tissues are removed in the process, they are usually not submitted for analysis. Thus, correct diagnosis is often delayed. The clinical similarities between peri-implant malignancy and PI, as well as the lack of awareness in the general dental profession of the possibility of malignancy imitating PI, may result in delayed diagnosis and compromised prognosis. Close examination of the cases with peri-implant malignancy for which clinical photographs have been provided in the literature, as well as the new cases in the present series, reveal that many malignancies resemble PI clinically at the time of diagnosis.^{28,29} Other examples, such as cases 4 and 5 in the present series, have presented changes in color, texture, and extent of lesions, which should have been recognized as suspicious and a biopsy performed, independent of the presence of implants. However, these cases initially exhibited only subtle signs that were interpreted as those of PI and only became suspicious with significant delay.

It is generally impossible to differentiate simple PI from its benign and malignant mimickers without proper histopathologic analysis. In cases assumed to be PI, an especially high suspicion level should be maintained in patients who have a history of predisposing conditions for oral cancer (previous oral malignancy, leukoplakia, erythroplakia, OLP, and PVL), since the majority of reported cases of peri-implant malignancy have occurred within this patient population. Smoking and alcohol abuse (a mean daily consumption of 13 g of ethanol or more) have been associated with an increased risk for oral and many other cancer types, so both should also be considered as indicators of risk in the context of peri-implant malignancy.⁴³ Patients with a recognized extraoral malignancy should also be observed with increased levels of suspicion, especially those with lung, colorectal, prostate, breast, and renal cancers, as these are the most common tumors reported to be the origins of metastatic tumors to the gingiva.²¹

In lesions that look like PI but do not respond well to conventional treatment or that progress, tissue should be submitted for microscopic evaluation without much delay. This would be beneficial not only for timely diagnosis of malignancy but also for correctly diagnosing lesions, such as giant cell granuloma, pyogenic granuloma, or actinomycosis, which exhibit potentially destructive behavior and may clearly influence implant survival.³

CONCLUSIONS

Peri-implant malignancy is not as rare as currently reported and may comprise up to 1.5% of oral malignancy cases. Its initial clinical presentation often

imitates PI and thus may cause delay in diagnosis. The majority of peri-implant malignancies occur in patients with pre-existing risk factors for oral cancer and in those with extraoral malignancy. In lesions suspected to be PI that fail to respond to conventional treatment or that progress, especially in the presence of a medical history that includes potentially malignant oral conditions, risk habits, and extraoral malignancy, the level of suspicion for malignancy should be increased, and tissue must be submitted for histopathologic evaluation.

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