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Abstract: The purpose of the present review was to integrate the available published data on peripheral giant cell granuloma (PGCG) associated with dental implants into a comprehensive analysis of its clinical/radiologic features. An electronic search was undertaken in February/2018 in three databases, looking for publications reporting cases of PGCGs associated with dental implants. Nineteen publications were included, reporting 37 implant-associated PGCG. These lesions are more prevalent in women, in mandible, and in posterior regions of the jaws. Both 'excision alone' and 'excision + curettage' presented high recurrence rates (40% and 31.3%, respectively). The etiology of implant-associated PGCG has not yet been determined. Despite the small number of cases reported, implant-associated PGCG shows a high recurrence rate (1/3) for a benign non-neoplastic lesion and sometimes it requires the removal of the associated implant in order to prevent further recurrences. This recurrence rate is not affected by curettage after excision.

Peripheral giant cell granuloma associated with dental implants: a systematic review

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ABSTRACT

The purpose of the present review was to integrate the available published data on peripheral giant cell granuloma (PGCG) associated with dental implants into a comprehensive analysis of its clinical/radiologic features. An electronic search was undertaken in February/2018 in three databases, looking for publications reporting cases of PGCGs associated with dental implants. Nineteen publications were included, reporting 37 implant-associated PGCG. These lesions are more prevalent in women, in mandible, and in posterior regions of the jaws. Both 'excision alone' and 'excision + curettage' presented high recurrence rates (40% and 31.3%, respectively). The etiology of implant-associated PGCG has not yet been determined. Despite the small number of cases reported, implant-associated PGCG shows a high recurrence rate (1/3) for a benign non-neoplastic lesion and sometimes it requires the removal of the associated implant in order to prevent further recurrences. This recurrence rate is not affected by curettage after excision.

KEYWORDS

Peripheral giant cell granuloma; giant cell lesion of the jaw; dental implant; complications; non-neoplastic proliferative lesions

INTRODUCTION

Peripheral giant cell granuloma (PGCG) is characterized by an unencapsulated proliferation of mononuclear spindle-shaped and polygonal cells with osteoclast-type multinucleated giant cells in a vascular background, occurring in the gingiva or alveolar mucosa [1]. Clinically, PGCG may present as a firm or soft nodule and as a sessile or pedunculated mass, confined to the alveolar and gingival mucosa. Different local causal factors have been associated with PGCG, including complicated dental extractions, dental restorations in poor condition, food impaction, dental malposition, plaque, and calculus [2]. PGCG has infrequently been reported as implant-associated soft tissue complications. Local irritation or a non-specified type of trauma may be contributing factors in the development of PGCG associated with dental implants [3,4]. The aim of the present study was to integrate the available data published in the literature on PGCG associated with dental implants.

MATERIALS AND METHODS

This study followed the PRISMA Statement guidelines [5].

Search strategies

An electronic search without time restrictions was undertaken in January 2018 in the following databases: PubMed/Medline, Web of Science, and Science Direct. The following terms were used in the search strategies:

((("peripheral giant cell granuloma") OR ("peripheral giant cell reparative granuloma") OR ("peripheral giant cell lesion") OR ("peripheral giant cell") OR ("peripheral giant cell epulis")) AND (dental implant OR oral implant)) NOT ("elastolytic giant cell granuloma")

Google Scholar was also checked. A manual search of all related oral pathology, maxillofacial and specialist dental and oral journals was performed. The reference list of the identified studies and the relevant reviews on the subject were also checked for possible additional studies. Publications with lesions identified by other authors as being PGCG, even not having the term “peripheral giant cell granuloma” in the title of the article, were also re-evaluated by one of the authors of the present study.

Inclusion and Exclusion Criteria

Eligibility criteria included publications reporting cases of PGCG associated with dental implants. The studies needed to contain enough clinical, radiological and histological information to

confirm the diagnosis. Hybrid tumors containing parts of PGCG were not considered for this study, as they may behave differently from non-hybrid PGCG.

The definitions and criteria of the World Health Classification of Tumors – Head and Neck Tumors book [1], were used to diagnose a lesion as PGCG. Other lesions or syndromic conditions presenting lesions with similar features, such as hyperparathyroidism, aneurismal bone cyst, cherubism, neurofibromatosis, Noonan syndrome or cases with reported altered levels of parathyroid hormone, calcium and phosphorus were excluded.

Study selection

The titles and abstracts of all reports identified through the electronic searches were read independently by the authors. For studies appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision, the full report was obtained. Disagreements were resolved by discussion between the authors. The clinical and radiological aspects, as well as the histological description of the lesions reported by the publications were thoroughly assessed by one of the authors (R.S.G.) of the present study, an Oral Pathologist, in order to confirm the diagnosis of PGCG.

Data extraction

The review authors independently extracted data using specially designed data extraction forms. Any disagreements were resolved by discussion. For each of the identified studies included, the following data were then extracted on a standard form, when available: year of publication, number of patients, patient's sex, age, lesion location (maxilla/mandible), anterior/posterior location (anterior: from canine to canine; posterior: premolars and molars region), lesion size, presence of marginal bone loss, time between implant surgery and appearance of the lesion, treatment performed, recurrence, recurrence period, removal or not of implant(s) associated with the lesion, and follow-up period. The lesion size was determined according to the largest diameter reported in the publications. Contact with authors for possible missing data was performed.

Analyses

The mean, standard deviation (SD), and percentages were presented as descriptive statistics. Pearson's chi-squared or Fisher's exact tests were used for categorical variables, depending on the expected count of events in a 2x2 contingency table. All data were statistically analyzed using the Statistical Package for the Social Sciences (SPSS) version 25 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Literature search

The study selection process is summarized in Figure 1. The search strategy in the databases resulted in 111 papers. Search in Google Scholar resulted in two eligible papers not found in the three main databases. A total of 33 articles were cited in more than one database (duplicates). The reviewers independently screened the abstracts for those articles related to the aim of the review. Of the resulted 80 studies, 57 were excluded for either not being related to the topic or not presenting clinical cases. Additional hand-searching of journals and of the reference lists of selected studies yielded no additional papers. The full-text reports of the remaining 23 articles led to the exclusion of 4 because they did not meet the inclusion criteria. Thus, a total of 19 publications were included in the review.

Description of the Studies and Analyses

Nineteen publications [3,6-11,4,12-22] were included, reporting 37 cases of implant-associated PGCG. Table 1 presents demographic and clinical features of all cases. The lesion was more prevalent in women than in men (24:13) in the mandible than in maxilla (25:12), and in posterior than in anterior regions (31:6). The mean age was 50.4 ± 13.6 years (min-max, 18-74). Information about the time between implant surgery and the diagnosis of the lesion was available for 19 lesions with a mean of 41.0 ± 36.9 months (min-max, 3-134). For the cases with available information, marginal bone loss was observed in 19 (82.6%) out of 23 cases. Nine out of 11 cases (81.8%) used implants with rough surfaces – there was no available information for the other cases. Lesion mean size was 1.59 ± 1.16 cm (min-max, 0.4-6.0; $n=32$). The implant was removed in 9 out of 26 cases (34.6%). All cases were treated by excision, and in 17/37 cases (45.9%) treatment was complemented by curettage of the subjacent bone. Nine out of 26 lesions (34.6%) recurred, after a mean time of 1.5 ± 1.7 months (min-max, 0.5-4.0; $n=4$). Multiple recurrences, from two to eight episodes, were reported in five patients. Five out of 16 lesions (31.3%) treated by excision followed by curettage recurred, while 4 out of 10 lesions (40%) treated by excision only recurred ($p = 0.483$; Fisher's exact test). The removal of the implant associated with lesion resulted in no further recurrences for the cases that presented three, four, and five recurrences – this information is not available for the cases with two and eight recurrences.

DISCUSSION

The aim of the present study was to integrate the available data published in the literature on PGCG associated with dental implants. A review of pathological conditions provides information

that can improve diagnostic accuracy, allowing pathologists and surgeons to make informed decisions and refine treatment plans to optimize clinical outcomes [23-26].

The present review showed that implant-associated PGCG are more prevalent in women and in the mandible. Most of the implant-associated PGCG cases presented in the posterior region of the jaws, and this can be explained by the fact that implants placed in the posterior regions pose a challenge for obtaining proper oral hygiene, which is a conditioning factor for the appearance of PGCG [10].

The etiology of dental implant-associated PGCG has not yet been determined because of the small number of reported cases. Complicated dental extractions, dental restorations in poor condition, food impaction, dental malposition, plaque, calculus [2], cement debris [8], unstable prostheses [19], and excessive proximity between implants [3] have been suggested as etiological factors. Many of the cases here reviewed were associated with marginal bone loss. It has been suggested that peri-implantitis and marginal bone loss expose the rough portion of the implant neck, which causes chronic irritation to the adjacent mucosa and may provoke the development of proliferative non-neoplastic reactive lesions such as PGCG [8]. Eighty percent of the cases here reviewed with available information occurred around implants of rough surface. All the nine implant-associated PGCG cases analyzed in one study [10] had foreign material embedded deep within the stroma, either isolated or surrounded by multinucleated giant cells. On the other hand, foreign material was found in only 43.5% of the tooth-associated PGCG cases. Halperin-Sternfeld et al. [10] suggested that inadvertent deposition of foreign bodies during implant placement plays a role in implant-associated PGCG pathogenesis. However, thousands of dental implants are placed daily, and there are very few reports published about PGCG or other tumor-like conditions associated with dental implants [8]. Furthermore, the clinicopathologic features of a foreign body reaction are very distinctive from giant cell lesions of the jaws. Still, we believe that the prevalence of implant-associated PGCG cases is underestimated, which might be influenced by the fact that, possibly, some professionals surgically excise peri-implant inflamed tissues and do not send it to histopathological examination. As it can be difficult to clinically differentiate between PGCGs and pyogenic granulomas, the definitive diagnosis based on the histology study is important [9].

Although PGCG etiopathology is not fully understood, it is recommended that patients rehabilitated with implants are fully instructed in matters of personal oral hygiene. Also, implant patients should attend close periodical maintenance programs. Dentists must be careful to avoid leaving foreign materials in the peri-implant tissues during the treatment, such as cement debris.

The implant-associated PGCG recurrence rate of 34.6% is considerably higher compared to PGCG not associated with dental implants, which is 9.5% [27]. Moreover, approximately half of the recurrent cases presented multiple recurrence episodes. Despite the limited number of implant-

associated lesions reported, our study shows an important difference regarding the clinical course of the lesions. The reason for this difference in recurrence rates is unclear, but it could be caused by lack of proper removal of the chronic irritating factors. Finally, the performance of curettage after excision seems to not affect the recurrence rate.

CONCLUSIONS

The etiology of implant-associated PGCG has not yet been determined. Despite the small number of cases reported, implant-associated PGCG shows a high recurrence rate (1/3) for a benign non-neoplastic lesion and sometimes it requires the removal of the associated implant in order to prevent further recurrences. This recurrence rate is not affected by curettage after excision.

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Declaration of conflicting interests

There are no conflicts of interest to declare.

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FIGURE CAPTIONS

Figure 1. Study screening process.

Figure 2. Histopathological aspect of a representative case of peripheral giant cell granuloma (PGCG). PGCGs are characterized by proliferation of mononuclear spindle-shaped and polygonal cells with osteoclast-type multinucleated giant cells in a vascular background (H&E staining, original magnification x10).

Authors	Year	Patient	Sex	Age	Implants involved (n)	Implant(s) localization	Implant(s) characteristics	Time since implantation (months)	Bone loss	Lesion size (cm)	1st treatment	Recurrence	Time of recurrence	Subsequent treatments	Implant loss / removal	Follow-up (months)	Observations
Hirshberg et al.	2003	1	M	31	1	Post mand	“Screw type”	Unknown	Yes	NA	Excision + curettage	Yes	NA	Excision (laser)	No	24	-
		2	M	69	1	Ant max	“Screw type”	14	Yes	NA	Excision + curettage	Yes	“Several months later”	Excision (laser)	Removal 6 months later (severe bone loss)	6	-
		3	F	44	1	46	“Screw type”	72	Yes	NA	Excision + curettage	Yes (3x)	NA	Excision (3x)	Removal in the last recurrence	NA	-
Bischof et al.	2004	1	F	56	1	35	Turned Brånemark, 3.75 x 18 mm	24	Yes	2.0	Excision + curettage	No	-	-	No	36	“The healing caps on 2 of the implants were partially unscrewed and in contact with each other, allowing dental plaque to accumulate. Calculus formed, preventing optimal oral hygiene maintenance.”
Cavezzi Junior	2004	1	F	42	1	24	NA	3	NA	NA	Excision	Yes	3 wk	Excision	Loss (3 months)	2	“One implant failed 3 months after surgery and was removed. Right after a lesion appeared in the region”
Cloutier et al.	2007	1	M	21	1	46	TPS Straumman	72	Yes	2.0 x 1.5	Excision + curettage	No	-	-	Removal together with the excision of the lesion	12	“There was no calculus accumulation or cement debris associated with the prosthesis or in the specimen submitted for histopathologic examination”
Scarano et al.	2008	1	F	48	1	24	3i	4	Yes	1.0	Excision + curettage	NA	-	-	No	NA	-
Hernandez et al.	2009	1	F	45	2	45, 46	Turned Brånemark, 3.75 x 7 mm	36	Yes	2.0 x 2.0	Excision + curettage	Yes (5x)	3 wk (1st)	Excision + curettage	Removal of one implant in the last recurrence	108	“Clinical examination of the abutments revealed no mobility or plaque accumulation.”
		2	F	36	1	16	TiUnite Brånemark, 4 x 13 mm	27	Yes	0.8	Excision + curettage	Yes (4x)	2 wk (1st), 1 mo (2nd) 2 mo (4th)	Excision + curettage	Removal in the last recurrence	12	” There was no plaque accumulation on the crown.”
		3	F	62	1	36	TiUnite Brånemark, 4 x 13 mm	3	Yes	2.0 x 2.0	Excision	No	-	-	No	2	One-stage approach
Özden et al.	2009	1	F	60	2	36, 37	Straumann	67	Yes	2.0 x 1.5	Excision + curettage	No	-	-	No	12	Patient went to dentist 6 years after implants, but the lesion had a 5-month

																	history. "The fixed prosthesis was not fully seated, resulting in poor marginal adaptation of the implants (...) which promoted plaque accumulation and soft tissue irritation"
Hanselaer et al.	2010	1	F	33	1	15	TiUnite Brånemark	36	No	NA	Excision + curettage	No	-	-	No	8	Cemented crown
Olmedo et al.	2010	1	F	64	1	22	"Brånemark-like", 4.1 x 11.5 mm	134	Yes	0.6 x 0.5	Excision + curettage	No	-	-	No	24	Patient went to dentist 12 years after implants, but the lesion had a 10-month history.
Peñarrocha-Diago et al.	2012	1	F	54	2	45, 46	TSA-surface Defcon Avantblast	36	Yes	2.0 x 2.0	Excision + curettage + "implantoplasty"	No	-	-	No	12	"Implantoplasty of the exposed implant threads was carried out using a 30-µm diamond drill fitted to a handpiece operating at 15 000 rpm"
Lester et al.	2014	1	M	68	1	Left max	NA	NA	NA	0.4 x 0.4	Incisional biopsy	No	-	-	No	NA	-
		2	F	18	2	34, 35	NA	NA	NA	1.8 x 1.0	Incisional biopsy	Yes (8x)	NA	NA	NA	NA	-
		3	F	70	1	46	NA	NA	Yes	0.5 x 0.4	Incisional biopsy	Yes (2x)	NA	NA	NA	NA	-
		4	M	68	NA	Ant mand	NA	NA	NA	1.1 x 0.6	Excision	No	-	-	No	NA	-
		5	F	49	2	35, 36	NA	NA	NA	0.6 x 0.3	Excision	No	-	-	No	NA	-
Brown et al.	2015	1	M	46	1	36	Titamax, Neodent	10	No	1.0 x 0.8 0.7 x 0.6	Excision	Yes	4 mo	Excision + curettage	No	12	-
Jané-Salas et al.	2015	1	M	64	1	46	NA	96	Yes	1.0 x 1.0	Excision + curettage	No	-	-	No	12	-
Ogbureke et al.	2015	1	M	44	2	46, 47	NA	3	No	4.5 x 2.5	Excision	NA	NA	NA	No	NA	-
Pacifici et al.	2015	1	M	60	1	12	NA	60	Yes	2.0 x 2.0	Excision + curettage	No	-	-	No	19	"The oral hygiene appeared to be poor."
Galindo-Moreno et al.	2016	1	M	74	1	14	Microdent System	72	No	2.5 x 2.0	Excision	No	-	-	No	6	-
Halperin - Sternfeld et al.	2016	9 patients	1M 8F	53±11	NA	Post max (1) Post mand (8)	NA	NA	NA	1.03±0.28	Excision	NA	NA	NA	NA	NA	-
Sezgin et al.	2016	1	F	52	1	25	NA	9	Yes	1.2 x 0.5	Excision	No	-	-	No	18	"residual cement were detected on the buccal aspect of the implant."
Scarano et al.	2018	1	M	26	1	43	NA	NA	Yes	1.5	Excision + peripheral	No	-	-	Removal together with	12	-

Figure 1
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Figure 2
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