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Peripheral giant cell granuloma: an updated analysis of 2824 cases reported in the literature

Running title: Peripheral giant cell granuloma: a review

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KEYWORDS

Peripheral giant cell granuloma; giant cell lesion; clinical features; treatment; recurrence rate

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ABSTRACT

Objective. To integrate the available data published on peripheral giant cell granuloma (PGCG) into a comprehensive analysis of its clinical/radiologic features.

Materials and Methods. An electronic search was undertaken in January/2018 in 5 databases, looking for publications reporting cases of PGCGs. Probability of recurrence was calculated for some variables.

Results. 165 publications were included, 2824 lesions identified. PGCGs were slightly more prevalent in women and more prevalent in mandibles, usually asymptomatic, and presenting erosion of the subjacent bone in almost 1/3 of cases. Additional curettage (2.8%) or peripheral osteotomy (0%) after excision presented lower recurrence rates in comparison to excision alone (16%). Excision followed by curettage decreases the probability of recurrence by 85% in comparison to excision alone. Other factors (age, lesion size, follow-up, gender, location, clinical symptoms, bone erosion) seem to do not influence the probability of recurrence.

Conclusions. As surgical excision alone shows a considerable recurrence rate, excision followed by an additional therapy - curettage or peripheral osteotomy - should be the first choice of treatment of PGCG.

KEYWORDS

Peripheral giant cell granuloma; giant cell lesion; clinical features; treatment; recurrence rate

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 Despite the fact the PGCG is a non-infiltrative peripheral lesion and generally of reduced size, considerable recurrence rates have been reported in some clinical series.²⁻⁵ The aim of the present study was to integrate the available data published in the literature on PGCG into an updated comprehensive comparative analysis of their clinical features, as well as to analyze the influence of several factors in the recurrence rate.

MATERIALS AND METHODS

This study followed the PRISMA Statement guidelines.⁶

Search strategies

An electronic search without time restrictions was undertaken in January 2018 in the following databases: PubMed/Medline, Web of Science, Science Direct, J-Stage, and Lilacs. 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")) NOT ("elastolytic giant cell granuloma"))

Google Scholar was also checked. A manual search of related journals, including *Acta Odontologica Scandinavica*, *Acta Oto-Laryngologica*, *Annals of Otology Rhinology and Laryngology*, *British Journal of Oral and Maxillofacial Surgery*, *Cancer*, *Head & Neck*, *Head and Neck Pathology*, *International Journal of Oral and Maxillofacial Surgery*, *Japanese Journal of Oral and Maxillofacial Surgery*, *Journal of Dental Research*, *Journal of Craniofacial Surgery*, *Journal of Cranio-Maxillofacial Surgery*, *Journal of Japanese Society of Oral Oncology*, *Journal of the Japanese Stomatological Society*, *Journal of Laryngology and Otology*, *Journal of Maxillofacial and Oral Surgery*, *Journal of Nihon University School of Dentistry*, *Journal of Oral and Maxillofacial Surgery*, *Journal of Oral Pathology and Medicine*, *Journal of the Stomatological Society*, *Laryngoscope*, *Oral Diseases*, *Oral Oncology*, *Oral Surgery Oral Medicine Oral Pathology Oral Radiology*, *Otolaryngology -- Head and Neck Surgery*, and *Quintessence International*, 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 an author of the present study.

Inclusion and Exclusion Criteria

Eligibility criteria included publications reporting cases of PGCG. The studies needed to contain enough clinical, radiological and histological information to confirm the diagnosis. Randomized and controlled clinical trials, cohort studies, case-control studies, cross-sectional studies, case series, and case reports were included. Exclusion criteria were immunohistochemical studies, histomorphometric studies, radiological studies, genetic expression studies, histopathological studies, cytological studies, cell proliferation/apoptosis studies, *in vitro* studies, and review papers, unless any of these publication categories had reported any cases with enough clinical, radiological and histological information. 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 (last updated in 2017), 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 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 expert in oral pathology, 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 and race, follow-up period, duration of the lesion previously to treatment, lesion location (maxilla/mandible), anterior/posterior location (three categories: [a] anterior: lesions in the incisors/canine region; [b] premolar region; [c] posterior: lesions in the molars/retromolar region), recurrence, recurrence period, lesion size, presence of erosion of the subjacent cortical bone presence of clinical symptoms, and treatment performed (excision, curettage, enucleation, marginal resection, other). 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. Kolmogorov–Smirnov test was performed to evaluate the normal distribution of the variables, and Levene's test evaluated homoscedasticity. The performed tests for two independent groups were Student's t-test or Mann-Whitney test, depending on the normality. 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. The probability of recurrence was calculated for some variables, whenever

possible, in odds ratio (95% confidence interval). The degree of statistical significance was considered $p < 0.05$. All data were statistically analyzed using the Statistical Package for the Social Sciences (SPSS) version 23 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Literature search

The study selection process is summarized in Figure S1 (*see Supplemental Appendix*). The search strategy in the databases resulted in 4461 papers. Search in Google Scholar resulted in 26 eligible papers not found in the five main databases. A number of 1125 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 3362 studies, 3163 were excluded for not being related to the topic or not presenting clinical cases. Additional hand-searching of journals and of the reference lists of selected studies did not yield additional papers. The full-text reports of the remaining 199 articles led to the exclusion of 34 because they did not meet the inclusion criteria. Thus, a total of 165 publications were included in the review (*see Supplemental Appendix*).

Description of the Studies and Analyses

165 publications reporting 2824 PGCGs were included in the present review. Table 1 presents demographic and clinical features of all cases. The lesion was more prevalent in women than in men, at a 1.2:1 proportion. The mean age of the patients was 36.9 ± 18.5 years (range 1-89), being more elevated in women. Figure 1 shows the distribution of the lesions according to age, with the highest prevalence in the fifth and then fourth decade of life. The lesions were more prevalent in the mandible in comparison to the maxilla, but there was no clear prevalence concerning the different regions of the jaws (Figure 2). The lesions had a mean size of 1.7 ± 0.9 cm (min-max, 0.4-6.2; $n=564$). 26 lesions were associated with dental implants. The race of the patient was reported in 1582 cases. 738 cases were diagnosed in Persians, 327 in Caucasians, 166 in Indians, 149 in Arabs, 139 in Turks, 31 in blacks, 23 in Hispanics, and 9 in Asians.

Time of follow-up was informed for 267 lesions, with a mean $\pm$ SD of 23.8 ± 25.6 months (min-max, 1-108). 63.3% of these lesions were followed up to 12 months, and 76.0% for up to 24 months. Treatment of the lesions was known in 1424 (out of 2774, 51.3%) cases, of which 98.1% of the cases consisted of surgical excision with or without an additional therapy – curettage or peripheral osteotomy. There were 144 recurrences (9.5%) in 1513 lesions. The interval from initial treatment to the first recurrence (information available for 19 out of the 116 recurrences) ranged from 0.5 to 48 months after treatment, with a mean interval of 9.5 ± 15.1 months. Only 3 out of these 19 lesions recurred past the 1-year post-treatment period, one 30 months and other two cases 48 months after

treatment. Table 2 shows the recurrence rate according to the treatment performed. Additional curettage (2.8%) or peripheral osteotomy (0%) after excision presented lower recurrence rates in comparison to excision alone (16%). Sclerotherapy had a 4.2% recurrence rate. Marginal resection (the case did not recur) and radiation (the case recurred) were performed in 1 case each.

Table 3 shows the recurrence rate according to the some variables. Excision followed by curettage decreases the probability of recurrence by 85% in comparison to excision alone. Other factors seem to do not influence the probability of recurrence.

Table 4 shows the type of excision performed in lesions of different size ranges. There was a statistically significant difference between the performance enucleation alone and of enucleation plus additional therapies (curettage and peripheral osteotomy) only between lesions of size 1.1-2.0 cm and >3.0 cm. In general, however, larger lesions were not more often treated with additional therapies (curettage or peripheral osteotomy) after excision than smaller lesions.

DISCUSSION

The aim of the present study was to integrate the available data published in the literature on PGCG into an updated comprehensive comparative analysis of their clinical features, as well as the frequency of recurrence. A review of pathological lesions is important because it provides information that can improve diagnostic accuracy, allowing pathologists and surgeons to make informed decisions and refine treatment plans to optimize clinical outcomes.⁷⁻⁹

The present review observed that PGCGs were slightly more prevalent in women and more prevalent in mandibles, usually asymptomatic, and presenting erosion of the subjacent bone in almost 1/3 of cases. As the great majority of lesions were treated by excision, with or without curettage, it is difficult to compare success or relapse between the different modalities. The rate of recurrence of 10% shows that treatment is sometimes neglected by the professional, and curettage or peripheral osteotomy after excision seems to have a positive effect. Thus, excision with an additional therapy (curettage or osteotomy) should be the first choice of treatment. There are few cases treated by sclerotherapy, but sometimes it does not represent definitive treatment. As the peripheral lesions are easily excised, we understand that sclerotherapy does not have the same utility as in central lesions.

Recurrences of PGCGs could be related to incomplete removal of the lesion. The lack of removal of the periosteum with the surgical excision could be related to a higher recurrence.⁵ As this information was rarely reported in the publications reviewed, it is not possible to make a proper analysis. Still, Mighell et al.⁵ reported that histopathologically incompletely excised lesions from their study did not always recur, indicating that partial excision may be sufficient in some cases. It seems that due to the slight invasion of the tumor in the bone, especially when erosion of the underlying

bone is present, remnants of the lesion may be left when only excision is performed, which may increase the chances of recurrence. 92% of the lesions that recurred in one study⁴ exhibited transection of lesional tissue at the deep base of the specimen.

Genetic mutations are not exclusive for neoplasms, being reported in proliferative conditions, such as pyogenic granuloma.¹⁰ Recently, mutations in cancer-related genes were reported in central giant cell lesions.¹¹ Although no driver genetic event in either central or peripheral giant cell lesions has been described, future studies should focus on the investigation of the molecular alterations in these lesions in recurrent and non-recurrent cases.

The results of our study have to be interpreted with caution because of its limitations. First, there is a difference in the number of cases being analyzed between tables 1 and 3, with far less cases in table 3. Most of the cases of PGCG described in the literature were reported in clinical series, and some of them contain hundreds of lesions, as the publication of Motamedi et al.¹² This kind of study does not usually inform the characteristics of each lesion separately, i.e. one by one, but as a group. In that way, it is possible to use the information provided by clinical series to calculate, for example, the global recurrence rate, how many lesions were present in men and women and so on. However, it is not possible to use these data to calculate the effect size – in this case odds ratio – because there is no separate information of each variable (age, sex, location, etc) for each lesion. Thus, there is no way to connect a reported recurrence with any of these factors. Therefore, only the lesions with detailed individual information – most of them reported in case reports – were used for the calculation of the effect size. Second, all included studies were retrospective reports, which inherently result in errors, with incomplete records. Third, many of the published cases had a short follow-up, which could have led to an underestimation of the actual recurrence rate. Almost 2/3 of the lesions were followed up to only 1 year. However, it is hard to define what it would be considered a short follow-up period to evaluate the recurrence of these lesions.

CONCLUSIONS

As surgical excision alone shows a considerable recurrence rate, excision followed by an additional therapy - curettage or peripheral osteotomy - should be the first choice of treatment of PGCG.

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Declaration of conflicting interests

There are no conflicts of interest to declare.

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FIGURE LEGENDS

Figure 1. Distribution of peripheral giant cell granulomas according to age (for the cases which the patients' age were informed, n=2122).

Figure 2. Topographical distribution of the known precise locations (n=563) of peripheral giant cell granulomas. Cases involving multiple regions (or an entire quadrant) are indicated between arrows. Numbers at the top and bottom of the lines indicate cases involving both adjoining regions: anterior/premolar, premolar/molar. For the rest of the lesions (n=2261), the location was the 'maxilla' (n=293), 'mandible' (n=385), 'anterior maxilla' (n=260), 'posterior maxilla' (n=236), 'anterior mandible' (n=370), 'posterior mandible' (n=441), and 'not available' (n=276).

Table 1. Demographic and clinical features of peripheral giant cell granuloma described in the literature.

Variables	
n	2824
Age (years), mean±SD (min-max)	36.9±18.5 (1-89; n=2720)
Men	35.1±19.4 (4-85; n=1043)
Women	38.1±17.7 (1-89; n=1223)
<i>p</i> value ^a	0.001
Gender, n (%)	
Men	1252 (45.4)
Women	1504 (54.6)
Unknown	68
Jaw, n (%)	
Maxilla	1026 (40.3)
Mandible	1522 (59.7)
Unknown	276
Symptomatic, n (%)	
Yes	35 (6.3)
No	522 (93.7)
Unknown	2217
Bone erosion, n (%)	
Yes	176 (28.2)
No	448 (71.8)
Unknown	2150
Treatment, n (%)	
Excision alone	772 (54.2)
Excision + curettage	618 (43.4)
Excision + peripheral osteotomy	8 (0.5)
Sclerotherapy	24 (1.7)
Marginal resection	1 (0.1)
Radiation	1 (0.1)

Unknown	1350
Recurrence, n (%)	
Yes	144 (9.5)
No	1369 (90.5)
Unknown	1311
Follow-up time (months), mean±SD (min-max)	23.8±25.6 (1-108; n=267)
Lesion size (cm), mean±SD (min-max)	1.7±0.9 (0.4-6.2; n=564)

SD – standard deviation

^a Comparison of the mean age between men and women (Mann-Whitney test)

Table 2. Treatment recurrence – for the lesions with available information about treatment and recurrence.

Treatment	
Recurrence/total (% recurrence)	
Excision alone	91/567 (16.0)
Excision + curettage	17/610 (2.8)
Excision + peripheral osteotomy	0/8 (0)
Sclerotherapy	1/24 (4.2)
Marginal resection	0/1 (0)
Radiation	1/1 (100)
TOTAL	110/1211 (9.1)

Table 3. Recurrence rate for peripheral giant cell granuloma according to different factors – for the lesions with available information about both recurrence and the factors here included.

Factor	Recurrence/total (% recurrence)	<i>p</i> value	Odds ratio (95% CI)	<i>p</i> value
<i>Excision</i>				
Alone	91/567 (16.0)		1	
+ curettage	17/610 (2.8)	<0.001 ^{a,b}	0.150 (0.088, 0.255) ^c	<0.001
+ peripheral osteotomy	0/8 (0)			
<i>Age</i>				
Increase by 1 year	-	-	0.989 (0.966, 1.012)	0.353
<i>Lesion size</i>				
Increase by 1 cm	-	-	0.800 (0.451, 1.420)	0.446
<i>Follow-up</i>				
Increase by 1 month	-	-	1.017 (0.987, 1.048)	0.266
<i>Gender</i>				
Men	12/79 (15.2)		1	
Women	8/82 (9.8)	0.296 ^a	0.604 (0.233, 1.567)	0.300
<i>Jaw</i>				
Maxilla	10/82 (12.2)		1	
Mandible	10/79 (12.7)	0.929 ^a	1.043 (0.409, 2.662)	0.929
<i>Symptomatic</i>				
No	13/108 (12.0)		1	
Yes	3/13 (23.1)	0.235 ^d	2.192 (0.533, 9.019)	0.277
<i>Bone erosion</i>				
No	3/32 (9.4)		1	
Yes	13/74 (17.6)	0.220 ^d	2.060 (0.544, 7.797)	0.287

CI - confidence interval

^a Pearson's chi-squared test

^b Significance of the difference of the recurrence rate between 'excision alone' and 'excision + curettage'

^c Odds ratio of the recurrence probability of 'excision + curettage' in relation to 'excision alone'

^d Fisher's exact test

Table 4. Type of excision performed in lesions of different size ranges.

Size (cm)	Excision			<i>p</i> value ^{a,b}
	Alone n (%)	+ curettage	+ peripheral osteotomy	
0-1.0	22 (71)	8 (25.8)	1 (3.2)	0.083 ^c
1.1-2.0	34 (52.3)	30 (46.2)	1 (1.5)	0.754 ^d
2.1-3.0	27 (67.5)	10 (25)	3 (7.5)	0.555 ^e
>3.0	21 (77.8)	4 (14.8)	2 (7.4)	0.125 ^f
				0.023 ^g
				0.360 ^h

^a Pearson's chi-squared test

^b For the comparison of prevalence between 'enucleation alone' and enucleation plus additional therapy ('+ curettage' and '+ peripheral osteotomy' considered together)

Significance of the difference of the treatment prevalence between lesions of:

^c 0-1.0 cm and 1.1-2.0 cm

^d 0-1.0 cm and 2.1-3.0 cm

^e 0-1.0 cm and >3.0 cm

^f 1.1-2.0 cm and 2.1-3.0 cm

^g 1.1-2.0 cm and >3.0 cm

^h 2.1-3.0 cm and >3.0 cm