Journal of Research in Medical and Dental Science
2022, Volume 10, Issue 6, Page No:213-218

Available Online at: www.jrmds.in
eISSN No. 2347-2367: pISSN No. 2347-2545

Clinicopathological and Immunohistochemical Comparison of Peripheral and Central Giant Cell Granuloma of the Jaws Using CD68 and CD 163

Sumaya Mohammed Mansor*, Ban F Al-drobie

Department of Oral Diagnosis, College of Dentistry, University of Baghdad, Iraq

ABSTRACT

Background: A tumor-like disease that affects the jawbone may develop either peripherally in the periodontal ligament and muco periosteum, peripheral giant cell granuloma (PGCG) or centrally in the bone "central giant cell granuloma" (CGCG).

Objectives: To evaluate the expression of CD68 and CD163 proteins in mononuclear cells and compare it between (CGCG) and (PGCG), in addition, to calculate to determine whether or not their expression levels may be utilized to distinguish amongst one another.

Methods: In order to conduct this study, we obtained 30 formalin-fixed paraffin-embedded tissue blocks from the archives of the oral pathology laboratory of the oral diagnostic department at the College of Dentistry/University of Baghdad/, with 15 for CGCG and 15 for the PGCG. Four- µm thick sections were cut from the blocks; one section was stained by eosin and hematoxylin for confirmation of diagnosis, and two sections were prepared for the Immunohistochemical identification of CD163 and CD68, as directed by the manufacturer's instructors.

Results: The expression levels of CD163 were higher in PGCGs than CGCGs, but there was no statistical difference regarding CD163 between CGCG and PGCG (P=0.294). While CGCGs expressed CD68 at greater levels than PGCGs, the statistical significance of the differences between the two groups could not be established. (P=0.771).

Conclusions: From a present study's findings, all the studied tissue specimens of giant cell lesions showed a positive Immunohistochemical expression of CD68 and CD163 antibodies, so it can be concluded that the Histogenesis of CGCG and PGCG was monocytes macrophage origin.

Key words: Peripheral giant cell granuloma, Central giant cell granuloma, CD68, CD163

HOW TO CITE THIS ARTICLE: Sumaya Mohammed Mansor, Ban F Al-drobie, Clinicopathological and Immunohistochemical Comparison of Peripheral and Central Giant Cell Granuloma of the Jaws Using CD68 and CD 163, J Res Med Dent Sci, 2022, 10 (6):213-218.

Corresponding author: Sumaya Mohammed Mansor

e-mail✉**:** ali.mario28@yahoo.com

Received: 02-May-2022, Manuscript No. JRMDS-22-62388;

Editor assigned: 04-May-2022, **PreQC No.** JRMDS-22-62388 (PQ);

Reviewed: 19-May-2022, QC No. JRMDS-22-62388;

Revised: 26-May-2022, Manuscript No. JRMDS-22-62388 (R);

Published: 02-June-2022

INTRODUCTION

The skull bones are affected by a set of distinct clinical entities known as "GC lesions of the craniofacial skeleton". These entities include "giant cell granuloma" (GCG), "giant cell tumor" (GCT), "aneurysmal bone cyst" (ABC), cherubism, and brown tumors associated with hyperparathyroidism [1].

A prevalent condition is GCG, previously known as a GC reparative granuloma. This disease mostly affects, but is not limited to, the jaws. Reactive hyperplastic lesions, GCGs are seen in the oral cavity and are linked to a variety of oral tissues. Different entities have been identified depending on location, origin and clinical progression; PGCGs (peripheral) and CGCGs (central) [2,3]. (PGCGs) are dental and edentulous reacting exophytic lesions of the gingival and alveolar mucosa. It is the most prevalent of the GC lesions of the jaws. Periosteum or the periodontal ligament (PDL) is the source of it following local irritation or chronic injury as reddish or purple nodule [4]. PGCG may develop at any age usually in the fifth and sixth decades of life, with a small tendency for females [5]. In the 2nd and 3rd decades of life, the (CGCG) an interosseous lesion occurs more often in the mandible than in the maxilla. Among women, the disease is more common than among men [4,6,7].

Based on clinical and radiological characteristics, aggressive and non-aggressive types of CGCG are categorized. In general, non-aggressive types are more common, have fewer or no symptoms and develop more slowly than aggressive ones. In the aggressive

kind it causes discomfort and fast development, producing enlargement and perforation of the cortical bone, tooth displacement and root resorption [8]. The histopathological characteristics of the two lesions (CGCG and PGCG) are almost similar. In both cases, many multinucleated large cells are seen in a fibroblastic, well-vascularized environment, along with cells that range in form from oval to spindle in shape. It is believed that these cells are composed of a heterogeneous population of macrophages and fibroblastic-like cells [4,9].

On the other hand, despite the fact that these lesions are marked by the appearance of multinuclear GCs, the Histogenesis of the GCs has not yet been determined [10-12]. Some researchers believe that the giant cells have Immunohistochemical properties that are similar to those of osteoclasts [10,11], while other researchers have suggested the origin of the phagocytic and endothelial cells of these cells [13,14]. It has also been revealed that mononuclear stromal cells play an essential role in the development of GCs [15,16]. The CD68 is indeed a transmembrane glycoprotein that is expressed on monocytes and macrophages and serves as a selective macrophage-monocyte marker. It is also a membrane protein that is associated with lysosomes. A high level of CD68 expression has been seen in giant cells in a number of investigations done on giant cell lesions, supporting the histiocytes/macrophage nature of MGCs and MCs [11,13,17-21].

"Class B of the scavenger receptor cysteine-rich (SRCR) superfamily" contains a cluster of differentiation 163 (CD163) antigens, which are expressed by cells of the macrophage lineage. Homeostasis and binding of Hemoglobin-Haptoglobin complexes are important functions of CD163 [22] and is monocyte/macrophage lineage-specific [23,24].

MATERIAL AND METHOD

There have been a total of thirty cases identified with GCG (fifteen instances of CGCG and fifteen cases of PGCG) that have been reported to the Oral Pathology Laboratory at the College of Dentistry, University of Baghdad, between 2012 and 2020. We recovered and analyzed tissue blocks that had been formalin-fixed and paraffin-embedded (incisional and excisional biopsies). Collection of clinical data (including age, gender, lesion location and duration as well as the kind of biopsy performed) as well as lab and surgical records were required. To examine the morphology of the tissue slices (4 μm), they were sliced and placed on positively charged slides. The sections were then stained with hematoxylin and eosin (H&E) to be seen under a light microscope. Also stained immuno-histochemically with antibodies to CD68 (ab199000, 1:200) and CD163 (ab199402, 1:100) using EXPOSE Mouse and Rabbit Specific HRP/DAB Detection IHC kit (ab236466, 15ml).

It was demonstrated that specificity of the Immunohistochemical signal was achieved by showing a brown granular DAB staining pattern within a specific tissue compartment for a specific antibody in positive control tissue sections according to the manufacturer's datasheets, and the absence of such staining pattern in negative control tissue sections according to the manufacturer's datasheets. To assess the overall effectiveness of all primary antibodies, five sample fields were picked for each tissue segment, viewed, and scored microscopically with a 400X objective; for each marker, the average percent of the five high power fields was determined. The Immunohistochemical staining for CD68 and CD163 antibodies was measured semi quantitatively and assigned into categories for each one, as follows: scoring: 0 when less than 10%; 1 between 11% -50%; and 2 when greater than 50% for both CD68 and CD163 [25].

RESULTS

Clinical description

From 6 to 56 years old of CGCG patient's, there was a mean age of 30.67 years, and a greater prevalence of patients under 25 years old. For PGCG, the relevant age was ranging between 10 and 80 years, with a mean age of (47.60) years and a greater incidence in the age group over 45 years. Men: women ratios were (1:2.7) in CGCG and (1:1.5) in PGCG, according to the data on gender distribution. CGCG and PGCG had more mandibular lesions than maxillary lesions, according to the research.

The findings of the research also revealed that the size of the lesion in the case of PGCG was 53% >5 cm and 20% <2 cm, while the size of the CGCG lesion was approximately 53% <2 cm and 20% >5cm. When particular clinical and demographic characteristics of the 2 investigated groups were compared, it was discovered that the mean age of patients and the mean size of lesions were significantly higher in the PGCGs group than in the CGCGs group, respectively. For more clarifications (Table 1).

Histopathological findings

Microscopically, Connective tissue stroma is extremely vascular, with chronic inflammatory cell infiltration and extravagated red blood cell influx, in CGCG and PGCG, Multinucleated osteoclast-like giant cells scattered across a densely vascularized subcutaneous stroma that contains two kinds of stromal cells: a polygonal macrophage-like cell and a spindle-shaped fibroblastic cell. The GCs may be clustered together or uniformly distributed across the lesions The no. of nuclei in a cell may range from a few to several dozens, and the size of these cells might vary dramatically from one condition to the next. An osteoid or osseous structure may be seen. The presence of focal hemorrhages is also possible (Figures 1 and 2).

Immunohistochemical findings

In CGCG the percentage of immunopositive stromal cells for CD163 with a mean of 40.46, and SD of ± 26.31. While in PGCG the percentage of immunopositive stromal cells for CD163 with a mean of 49.86 and SD of ± 21.57. The comparison in mean expression between the two groups

Table 1: Comparison between the study groups by clinical and demographic characteristics.

Characteristics	The study groups		P–Value
	CGCGs Group (Mean ± SD)	PGCGs Group (Mean ± SD)	
Age (Years)	30.67 ± 18.44	47.60 ± 17.94	0.017
Size of Lesion (cm)	2.92 ± 1.90	4.81 ± 1.96	0.012
Duration of Lesion (Months)	9.53 ± 11.37	12.93 ± 9.52	0.394
	No. (%)	No. (%)	
Gender			
Male	4 (26.7)	6 (40.0)	0.438
Female	11 (73.3)	9 (60.0)	
Site of Lesion			
Mandible	12 (80.0)	11 (73.3)	0.425
Maxilla	3 (20.0)	4 (26.7)	
Location in Jaw			
Anterior	4 (26.7)	7 (46.7)	0.339
Premolar and Molar	9 (60.0)	5 (33.3)	
Posterior	2 (13.3)	3 (20.0)	

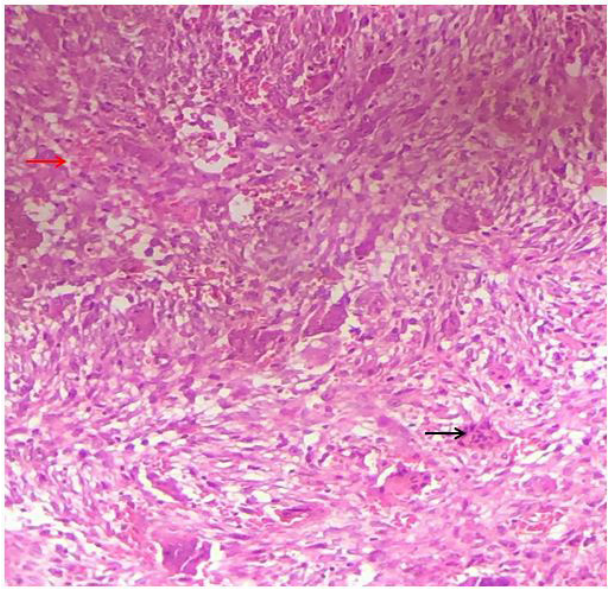

Figure 1: Photomicrograph showing giant cells (red arrow) in the background of stromal cells with areas of hemorrhage(red arrow) in central giant cell granuloma (CGCG) (H&E, X400).

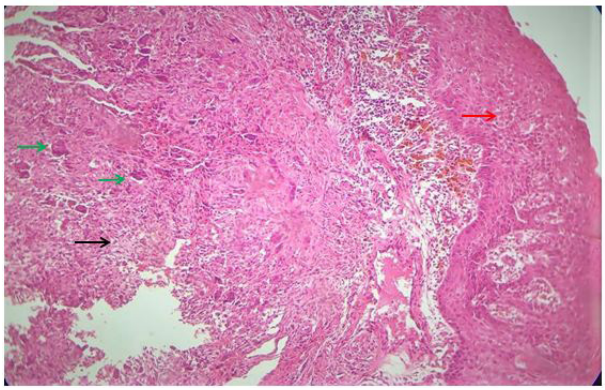

Figure 2: Photomicrograph showing surface stratified squamous epithelium (red arrow). The underlying connective tissue shows numerous giant cells (green arrow) in the background of mononuclear stromal cells (black arrow) in peripheral giant cell granuloma (PGCG) (H&E stain, x100).

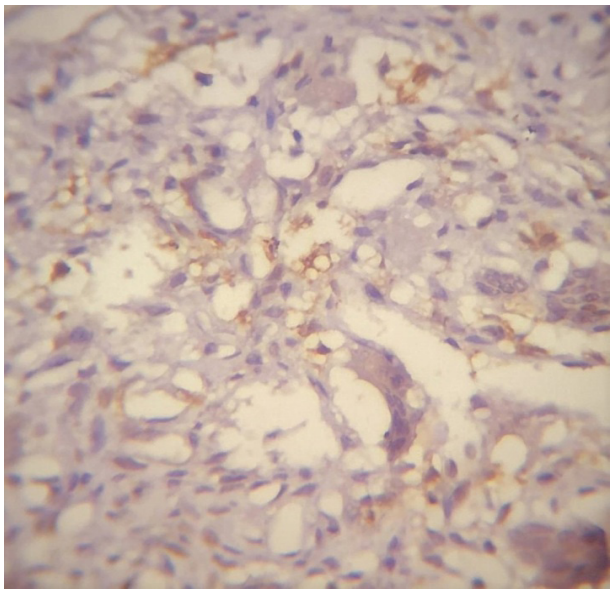

Figure 3: Immunohistochemical staining of CD68 marker. (CD163; x400) in mononuclear cells of central giant cell granuloma.

revealed that the expression levels of CD163 were higher in PGCGs than CGCGs, but this was in the mean of statistics non-significant (P=0.294). (Figures 3 and Figure 4).

All cases were CD68 positive, with positivity varying from 60% to 100%, with a mean of 85.86 and SD 14.44 in PGCG and a mean of 87.33 and SD 12.51 in CGCG, brown staining of stromal cells in both CGCG and PGCG. The expression levels of CD68 were higher in CGCGs than PGCGs, but there was no statistical difference (P=0.771) found in the mean expression of CD68 among the two groups (Figures 5 and Figure 6).

DISCUSSION

When it comes to the jaws, there is limited understanding of PGCL and CGCL. It is a contentious issue since the lesions may be confused with other jaw lesions both

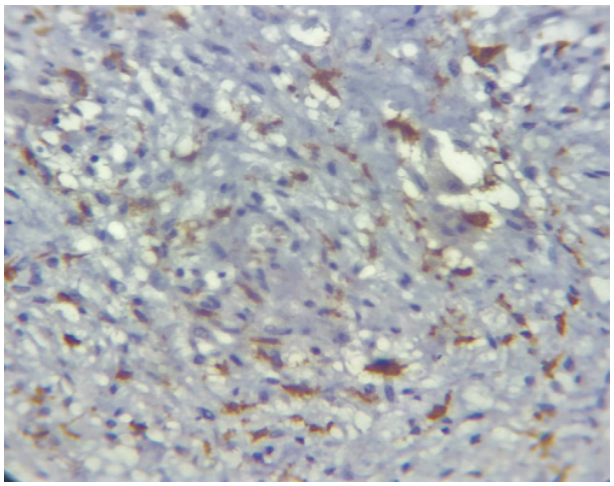

Figure 4: Immunohistochemical staining of CD68 marker. (CD163; x100) in mononuclear cells of peripheral giant cell granuloma.

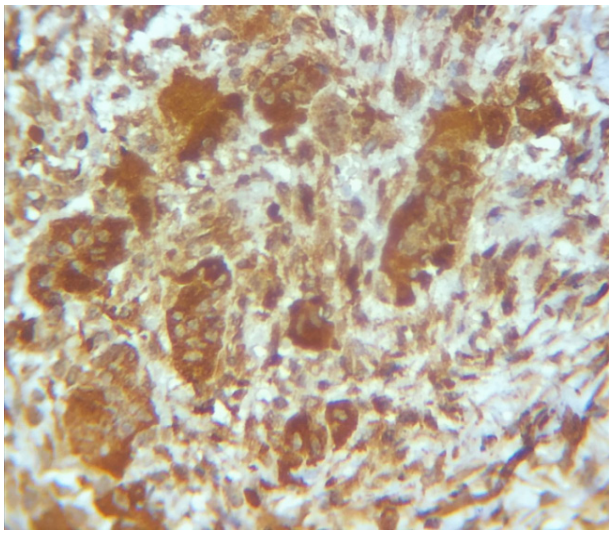

Figure 5: Immunohistochemical staining of CD68 marker (A) (CD68; x400) and CD163 marker.

radiologically and histologically, which is a source of contention [2]. Despite this, it is widely acknowledged that they behave in a clinically distinct manner. Knowing their natures and origins is very important in order to provide proper therapy for these conditions [2,3,26]. In the current study for CGCG patients revealed an age range from 6-56years with age mean of (30.67) years at the time of diagnosis; this finding was agreed with the previous study done by Omar A et al [27]. The peak incidence is 40% below the 25years reported in the presented study; this finding agrees with previous studies by Gnepp et al. and Neville et al. [1,7] in which the peak incidence and majority occurred in the young adult age group below 30years.

For PGCG comparable age range found in this study from 10-80years with an age mean of (47.60) years. Data from other reviews like, Neville et al and Omar et al was reported a similar age range [7,27]. The peak incidence and majority occurred in the current research in the age group above 45 years, with around 60% of this age group

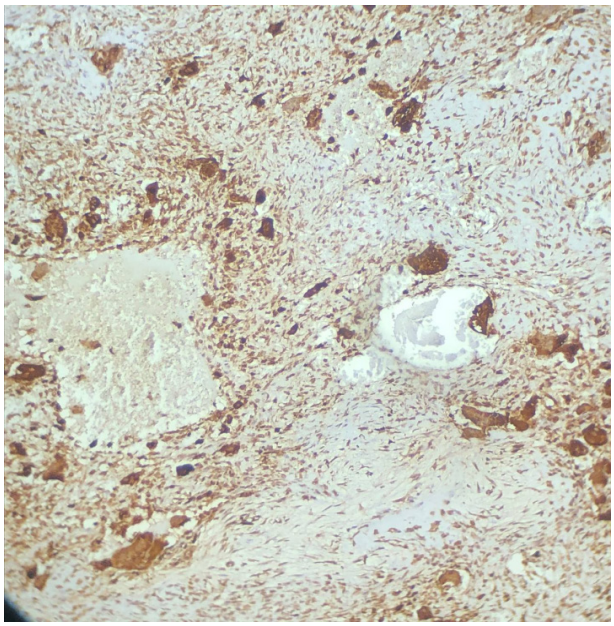

Figure 6: Immunohistochemical staining of CD68 marker (A) (CD68; x100) and CD163 marker.

being similar to that of a prior study age range from two to eighty five years, although the previous study discovered a peak was in the 6th decade of life, according to Motamedi et al. [4]. Furthermore, the age range in another research was from 6 to 88 years, with the mean age being 46 and rising frequency during the seventh decade of life [28]. In the sex distribution context, in this study, sex distribution revealed higher female propensity than male, with male-to-female proportion being (1: 2.7) in CGCG and male-to-female proportion being (1:1.5) in PGCG. This finding agrees with studies based on the data available in the literatures that revealed higher female propensity in both CGCG &PGCG [1,7,27,29-31]. On the contrary, another study performed by Lester et al found that both genders had approximately equal distribution [28].

Considering the site location of (GCG) in the jaws, this research reveals a high occurrence of the lesion in the mandible than in the maxilla. This finding agrees with previous studies [1,7,29,32] but disagrees with the study conducted by Omar A et al [27], which showed an equal distribution in maxilla and mandible.

In the context of the size of PGCG in the present study, about 53% >5 cm and about 20% <2cm, which disagrees with the study displayed by Neville et al [7] that demonstrated that the majority of tumors had a diameter of less than 2 centimeters. However, Kaya et al. revealed two cases of massive GCG of about 40 mm × 20 mm in diameter that attain bone resorption. PGCG of about 5 cm is also reported in the literature [33]. On the contrary, the size of CGCG in the present study was about 53% <2 cm and about 20%>5cm, which disagrees with the study by Neville et al [7]. The lesion may vary from a 5 mm incidental radiographic finding to a lesion that is more than 10 centimeter wide.

In the present study, when looking at CGCG and PGCG immuno-histochemically, the majority of the mononuclear stromal cell showed Immunohistochemical expression of CD163, which is agreed with the results of the study conducted by Kahn et al [34]. As they stated, CD163 expression is limited to cells of the macrophage lineage, which are mostly observed in perivascular sites. And also, according to Ghaly et al. [35]. The results of the current study showed percentage of immunopositive stromal cells with a mean of 40.46 in CGCG and 49.86 in PGCG The comparison in mean expression of CD163 between the two groups revealed that the expression levels of CD163 were higher in PGCGs than CGCGs, but there was no statistical difference (P=0.294), which disagreed with the study conducted by Ghaly et al. [35], that showed a statistically significant difference in macrophages CD163 expression between CGCG and PGCG. In the current study, all cases showed CD68 positivity with variable expression from one case to another. In the present study, a CD68 positive mononuclear cell showed in CGCG mean and is (87.33) and PGCG means (85.86 ± 14.44). The expression level in the mean is higher in CGCG than in PGCG, but there was no statistical difference in the proportion of stained between CGCG and PGCG, P=0.771. The findings of the present study showed some mononuclear cells of both peripheral and central GCG were positive for both CD163 and CD68, and probably, it can be said that GCs and mononuclear cells exhibit histolytic features.

CONCLUSION

The clinical and histological characteristics of CGCGs are similar to those of PGCGs. All the studied tissue specimens of giant cell lesions showed a positive Immunohistochemical expression of CD68 and CD163 antibodies. Thus, we can conclude, although macrophages have an essential part in the pathogenesis of giant cell lesions. There was no statistically significant difference in proportion of stained among CGCG and PGCG for CD68 immune marker and also there was no statistically significant difference in proportion of stained among CGCG and PGCG for CD163.

ETHICAL APPROVAL

College of Dentistry at the University of Baghdad has authorized all of our experiments. In accordance with the authorized protocols, all tests were carried out. (Ref no.270 on 25/3/2021).

FINANCIAL SUPPORT

There was no financial support.

CONFLICT OF INTEREST

There were no conflicts of interest.

REFERENCES

1. Gnepp DR, Bishop JA. Gnepp's diagnostic surgical pathology of the head and neck E-Book. Elsevier Health Sciences 2020.
1. Falci SG, Mesquita AT, Andrade BA, et al. FASN expression, angiogenesis and lymphangiogenesis in central and peripheral giant cell lesions. J Appl Oral Sci 2014; 22:131-137.
2. Kashyap B, Reddy SP, Desai R, et al. Computer assisted histomorphologic comparision and the expression of AgNORs in the central and peripheral giant cell lesions of the oral cavity and giant cell tumor of the long bone. J Oral Maxillofac Pathol 2014; 18:S54.
3. Motamedi MH, Eshghyar N, Jafari SM, et al. Peripheral and central giant cell granulomas of the jaws: A demographic study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007; 103:39-43.
4. Zargaran M, Moghimbeigi A, Afsharmoghadam N, et al. A comparative study of cathepsin D expression in peripheral and central giant cell granuloma of the jaws by immunohistochemistry technique. J Dent 2016; 17:98-104.
5. De Corso E, Politi M, Marchese MR, et al. Advanced giant cell reparative granuloma of the mandible: radiological features and surgical treatment. Acta Otorhinolaryngol Ital 2006; 26:168.
6. https://www.elsevier.com/books/oral-and-maxillofacial-pathology/neville/978-1-4557-7052-6
7. Reddy V, Saxena S, Aggarwal P, et al. Incidence of central giant cell granuloma of the jaws with clinical and histological confirmation: An archival study in Northern India. Br J Oral Maxillofac Surg 2012; 50:668-672.
8. Liu B, Yu SF, Li TJ. Multinucleated giant cells in various forms of giant cell containing lesions of the jaws express features of osteoclasts. J Oral Pathol Med 2003; 32:367-375.
9. Khiavi MM, Aghbali AA, Halimi M, et al. Immunohistochemical expression of Src protein in peripheral and central giant cell granulomas of the jaws. J Oral Maxillofac Pathol 2013; 17:358.
10. Torabinia N, Razavi SM, Shokrolahi Z. A comparative immunohistochemical evaluation of CD68 and TRAP protein expression in central and peripheral giant cell granulomas of the jaws. J Oral Pathol Med 2011; 40:334-337.
11. Patil KP, Kalele KP, Kanakdande VD. Peripheral giant cell granuloma: A comprehensive review of an ambiguous lesion. J Int Clin Dent Res Organization 2014; 6:118.
12. Varsha VK, Hallikeri K, Girish HC, et al. Expression of CD34 and CD68 in peripheral giant cell granuloma and central giant cell granuloma: An Immunohistochemical analysis. J Oral Maxillofac Pathol 2014; 18:341.
13. Tiffee JC, Aufdemorte TB. Markers for macrophage and osteoclast lineages in giant cell lesions of the oral cavity. J Oral Maxillofac Surg 1997; 55:1108-1112.
14. Flanagan AM, Tinkler SM, Horton MA, et al. The multinucleate cells in giant cell granulomas of the jaw are osteoclasts. Cancer 1988; 62:1139-1145.
15. Bonetti F, Pelosi G, Martignoni G, et al. Peripheral giant cell granuloma: Evidence for osteoclastic differentiation. Oral Surg Oral Med Oral Pathol 1990; 70:471-475.
16. Holness CL, Simmons DL. Molecular cloning of CD68, a human macrophage marker related to lysosomal

glycoproteins. Blood 1993; 81:1607-1613.

17. Carvalho YR, Loyola AM, Gomez RS, et al. Peripheral giant cell granuloma. An immunohistochemical and ultrastructural study. Oral Dis 1995; 1:20-25.
18. O'Mailey M, Pogrel MA, Stewart JC, et al. Central giant cell granulomas of the jaws: phenotype and proliferation-associated markers. J Oral Pathol Med 1997; 26:159-163.
19. Osterne RL, Matos-Brito RG, Alves AP, et al. Oral granulocytic sarcoma: A case report. Med Oral Patol Oral Cir Bucal 2009; 14:232-235.
20. Sargolzaei S, Taghavi N, Poursafar F. Are CD68 and Factor VIII-RA expression different in central and peripheral giant cell granuloma of jaw: An Immunohistochemical comparative study. Turk Patoloji Derg 2017; 1:49-56.
21. Fabriek BO, Dijkstra CD, van den Berg TK. The macrophage scavenger receptor CD163. Immunobiol 2005; 210:153-160.
22. Fonseca JE, Edwards JC, Blades S, et al. Macrophage subpopulations in rheumatoid synovium: Reduced CD163 expression in CD4+ T lymphocyte–rich microenvironments. Arthritis Rheumatism 2002; 46:1210-1216.
23. Nguyen TT, Schwartz EJ, West RB, et al. Expression of CD163 (hemoglobin scavenger receptor) in normal tissues, lymphomas, carcinomas, and sarcomas is largely restricted to the monocyte/macrophage lineage. Am J Surg Pathol 2005; 29:617-624.
24. Barbosa NG, Sá MC, Pinto LP, et al. Immunohistochemical study of macrophages subpopulations associated with squamous cell carcinoma of the tongue, with and without metastasis. J Br Patol Med 2015; 51:415-421.
25. Yadav S, Singh A, Kumar P, et al. Recurrent case of central giant cell granuloma with multiple soft tissue involvement. National J Maxillofac Surg 2014; 5:60.
26. https://pesquisa.bvsalud.org/portal/resource/pt/emr-104815
27. Lester SR, Cordell KG, Rosebush MS, et al. Peripheral giant cell granulomas: a series of 279 cases. Oral Surg Oral Med Oral Pathol Oral Radiol 2014; 118:475-482.
28. Sadri D, Shahsavari F, Hezarkhani M, et al. Expression of CD34 and CD31 in central and peripheral giant cell granulomas. J Dent 2019; 20:10.
29. Stavropoulos F, Katz J. Central giant cell granulomas: A systematic review of the radiographic characteristics with the addition of 20 new cases. Dentomaxillofac Radiol 2002; 31:213-217.
30. Katsikeris N, Kakarantza-Angelopoulou E, Angelopoulos AP. Peripheral giant cell granuloma. Clinicopathologic study of 224 new cases and review of 956 reported cases. Int J Oral Maxillofac Surg 1988; 17:94-99.
31. Mourad SI, Awad S, Shamaa A. Vascularity and angiogenesis level correlations with the clinical behavior of the central and peripheral giant cell granulomas of the oral cavity. Egyptian Dent J 2019; 65:2209-2218.
32. Kaya GŞ, Yalçin E, Tozoğlu Ü, et al. Huge peripheral giant cell granuloma leading to bone resorption: A report of two cases. Cumhuriyet Dent J 2011; 14:219-224.
33. Kahn A, Chaushu G, Ginene L, et al. Age and expression of CD163 and colony-stimulating factor 1 receptor (CD115) are associated with the biological behavior of central giant cell granuloma. J Oral Maxillofac Surg 2017; 75:1414-1424.
34. Ghaly AM, Gaballah ET, Elnagdy SY, et al. Comparing proliferative activity of giant cell granuloma lesions with osteoclastic and histiocytic derivation using PCNA, TRAP and CD163. Significance 2020; 677:833.