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A Comparative Analysis of Angiopoietin-like 4 (ANGPTL4) Immunohistochemical Expression in Giant Cell Granulomas of the Oro-maxillofacial Region and its Relation to the Clinicopathological Features.

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ABSTRACT
Background:The giant cell granulomas (GCG) are a group of localized reactive proliferative lesions associated with various tissues in the oral cavity. Two main entities have been described clinical-radiologically; the central (CGCG) occurring within the bone and the peripheral (PGCG) involving the gingiva or edentulous alveolar process (Cawson, 2013).They consist of multinucleated giant cells in a background of fibrous connective tissue with abundant spindle-shaped mononucleated cells (de Lange et al. 2007).Although CGCG & PGCG have similar histopathological features yet, they are reported to show different biological behavior with the peripheral has a better prognosis.
Objective: The present work wascarried out to reveal the possible relation between the ANGPL4 expression and the biological behavior of the types of GCG lesions.
Material and methods:Routine hematoxylin and eosin staining on thirty paraffin blocks of giant cell granuloma tissues to verify the diagnosis.Immunohistochemical staining was also used to analyze the expression of ANGPTL4in these cases.
Results: The intensity and the percentage of ANGPT4 in the current cases werelow to moderate reactions.
Conclusion: The biological behavior and the prognostic significance of GCGscanbe predicted from the expression of ANGPTL4.Also, further investigations should be made.

I. INTRODUCTION

Central giant cell granuloma (CGCG) is an uncommon, histologically benign but locally aggressive and destructive osteolytic lesion of osteoclastic origin that occurs in the craniofacial region, especially in jaw bones (Dimitakopoulos, Lazaridis, and Asimaki 2006). Lesions of central giant cell granuloma (CGCG) are classified as aggressive or non-aggressive. Non-aggressive lesions are asymptomatic, slow growing and radiographically radiolucent (unilocular and multilocular). However, the histologic differences between aggressive and nonaggressive GCLs are insufficient for pathologists to differentiate them (Peacock, Resnick, et al., 2012). Peripheral giant cell granuloma (PGCG) is the most common oral giant cell lesion that originates from the connective tissue of the periosteum or the periodontal membrane (Jindal et al. 2019).. Interspersed within the connective tissue are multinucleated giant cells resembling osteoclasts with numerous capillaries often present at the periphery of the lesion. In addition, inflammatory infiltrate containing polymorph nuclear cells, lymphocytes, and plasma cells is commonly seen in the tissue (Cawson 2013)(Troncone and Vigliar 2021)(Neville 2023). Several studies tried to reveal the factors driving the difference in the biological behavior of these lesions. Among these factors are proliferation and angiogenesis. More recently, the angiogenesis factors were thought to be involved in the process focontrolling the growth and behavior of the GCG lesions (Peacock, Jordan, et al., 2012; Sadri et al., 2019). Angiopoietin-like 4 Protein (ANGPTL4), a member of the angiopoietin-like family, is a secreted protein closely related to angiogenesis as well as lipid metabolism.

Objectives

The present work was carried out to reveal the possible relation between the ANGPL4 expression and the biological behavior of the GCGs

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of the jaws through studying the expression of ANGPL4 in these lesions.

II. MATERIAL AND METHODS:

Tissues:

The present retrospective study was carried out on selected thirty paraffin blocks of giant cell granuloma tissues(10 ACGCG, 10 NACGCG, and 10 PGCG) collected from the Oral Pathology Department, Faculty of Dentistry, Mansoura University.

Immunohistochemical marker:

Angiopoietin like_4 (ANGPTL4 Rabbit pAb), Catalog No: A2011

µl of concentrated antibody. Provided as a vial containing 50

The recommended dilution was 1:100. The Antibody was obtained from ABclonal Company.

Methods:

-Demographic as well as clinical data of all studied cases were collected from the recorded patients' reports regarding age, gender, site, and pain.

-Routine hematoxylin and eosin stainingto regard the GCGs.

-Immunohistochemical staining with the ANGPTL4 antibodywas also used to analyze the expression of iton these cases.

Evaluation and scoring of immunohistochemical reaction:

The other paraffin section was cut for immunostaining of the antibody: ANGPTL4. Sections were then mounted on Opti plus slides that were electrically charged to allow adhesion between the tissue sections and the slide surfaces. For each section, all the following procedures were performed at room temperature according to the manufacturer's instructions.

Specimens were considered to be positively stained when the reactive cells had a brown stain. The studied sections were evaluated by scoring the intensity of the membranous and/ or cytoplasmic staining for the ANGGPTL4. All stained slides have been independently evaluated by two reviewers.

The specimens were evaluated by two methods:

a. subjective evaluation
b. computer-assisted digital image analysis of the color intensity.

Subjective evaluation of the staining intensity (Nie et al. 2019)**:**

The ANGPTL4 expression was quantified by using asystem that considered both the ratio of positive cells and the staining intensity. The marks for the ratio of positive cells were 0 (≤5%), 1 (6-25%), 2 (26-50%), and 3 (>50%). The marks for staining intensity were 0 (undetectable), 1 (weak), 2 (medium), and 3 (strong). The two marks were summed up to obtain the final marks. A final mark of 0-3 was regarded as low expression, whereas a final mark of ≥4 was considered high expression.

Computer-assisted digital image analysis (digital morphometric study) (Kolb et al. 2019)

Slides were photographed using a MIC-W16 digital camera installed on a MEIJI MX5200L microscope, using a 20 X objective. The resulting images were analyzed on Intel® core I7® based computer using Fiji ImageJ (version 1.51r; NIH, Maryland, USA) software. For measuring the staining surface area, the color deconvolution 2 plugin was used. Five random fields from each slide were analyzed and a mean was calculated for each section.

III. RESULTS:

1-Clinical results and Histopathological results:

The age of the present series ranged between 6 and 67 years.The comparison between the age range of the three groups showed no statistical significance. Among the currently studied series, there was a slight female predilection. Little variation was found among the studied groups, with a statistically insignificant difference Among the current series, about two-thirds of the cases were encountered in the lower jaw in all groups. However, this distribution was not statistically significant (p=0.904).Regarding pain, most of the cases of PGCG and non-aggressive CGCG didn't express any pain, while aggressive CGCG cases were reported as painful. However, there was no statistically significant difference between groups (p=0.05).Cellular cannibalism appeared in all CGCGs and 80% of PGCGs. The occurrence of cannibalistic MNGCs among the aggressive group showed a median of 19.5 cellswhich was significantly higher than the non-aggressive and the peripheral groups(table 1).

Fisher's exact test showed that there was a significant association between the presence of the capsule and the peripheral type of giant cell lesion, p<0.0001.Microscopically, all of the CGCG were non-encapsulated, with no overlying surface epithelium. The MNGCs were prominent and showed irregular distribution varying between focal and even in the same section (Figure 1). In the non-aggressive type, MNGCs were prominent and focally distributed around areas of hemorrhage and blood vessels in all cases,(Figure 2). PGCGs were mostly observed to be covered by hyperplastic stratified squamous epithelium with thin and long rete processes, and cell-free zone subepithelial

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while MNGCs were focally distributed around areas of hemorrhage with abundant eosinophilic cytoplasm in all the subjects (figure 3,4). Cellular cannibalism appeared in 80% of PGCGs (figure 5) (table 2).

Table (1): Clinical and histopathological data of the studied groups:

	ACGCG N=10(%)	NACGCG N=10(%)	PGCG n=10 (%)	p value
Age/years mean±SD	34.8	39.4	40.3	0.7734
Sex **Male** **Female**	 6(60) 4(40)	 3(30) 7(70)	 5(50) 5(50)	0.534
Site **Mandible** **Maxilla**	 6(60) 4(40)	 6(60) 4(40)	 6(60) 4(40)	>0.904
Pain **absent** **present**	 7(70) 3(30)	 1(10) 9(90)	 9(90) 1(10)	0.05*
Cellular cannibalism **Median** **Range**	19.5 (11-30)	 9.5 (8-18)	 4 (1-8)	P<0.001*

Table 2: Histopathological results in the studied GCG groups:

n=10/group	Features		ACGCG	NACGCG	PGCG	P value
	Capsule	Absent	10	10	2	=<0.0001*
		Present	0	0	8	
	MNGCs distribution	Focal	0	10	10	= 1
		Even	10	0	0	
	Bone trabeculae	Absent	6	7	6	= 1
		Present	4	3	4	
	Cellular lacunae	Absent	3	2	5	= 0.49
		Present	7	8	5	
	Stroma (Cellular component)	Low	2	6	6	= 0.69
		High	8	4	4	
	Stroma (Fibrous component)	Delicate	6	4	3	= 0.53
		Dense	4	6	7	

Used test: Fisher's Exact Test.*: significant between studied GCG group at $p < 0.05$

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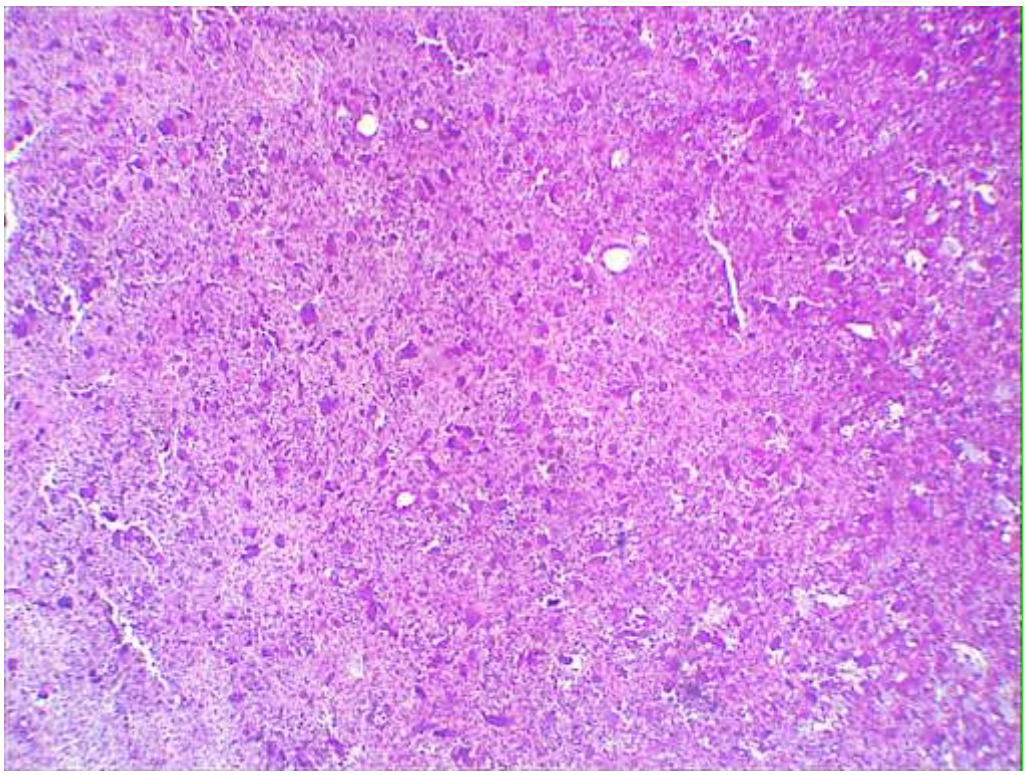

Figure1: Photomicrograph of aggressive CGCG showing the irregular distribution of MNGCs (H&Ex40).

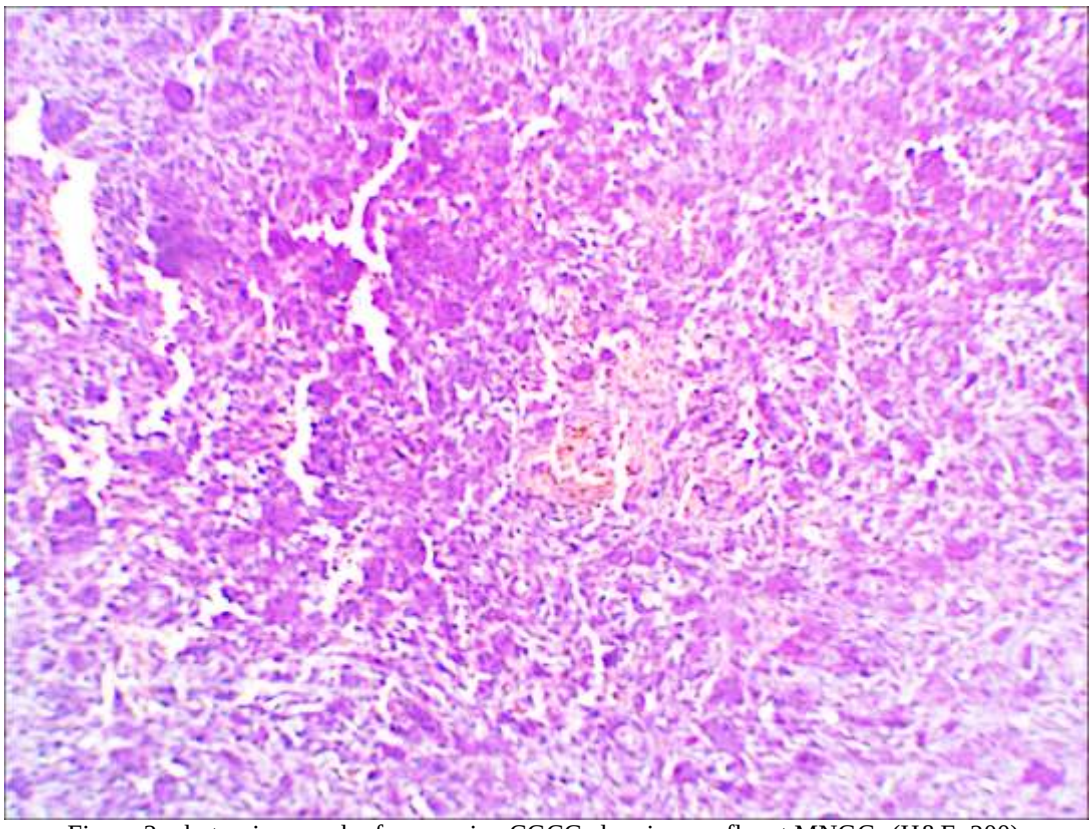

Figure 2: photomicrograph of aggressive CGCG showing confluent MNGCs (H&Ex200).

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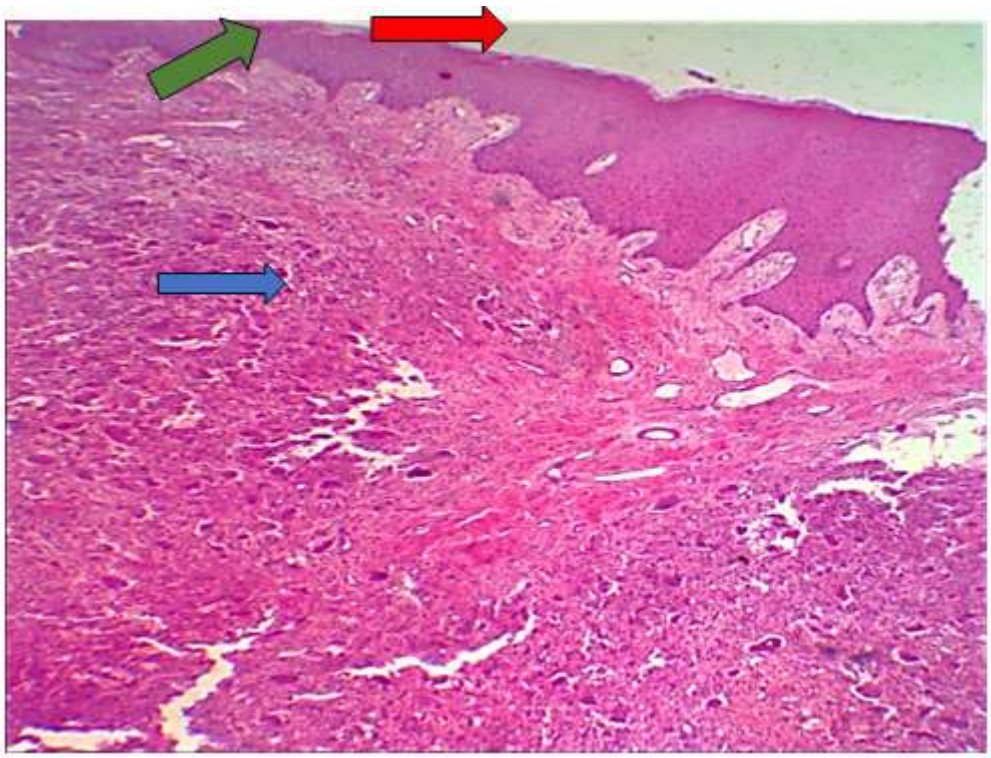

Figure (3): Photomicrograph of PGCG showing surface stratified squamous epithelium (red arrow), and focal aggregation of MNGCs (blue arrows). The immediate subepithelial C.T. is devoid of GCs forming the Grenz zone (green arrow) (H&E x40)

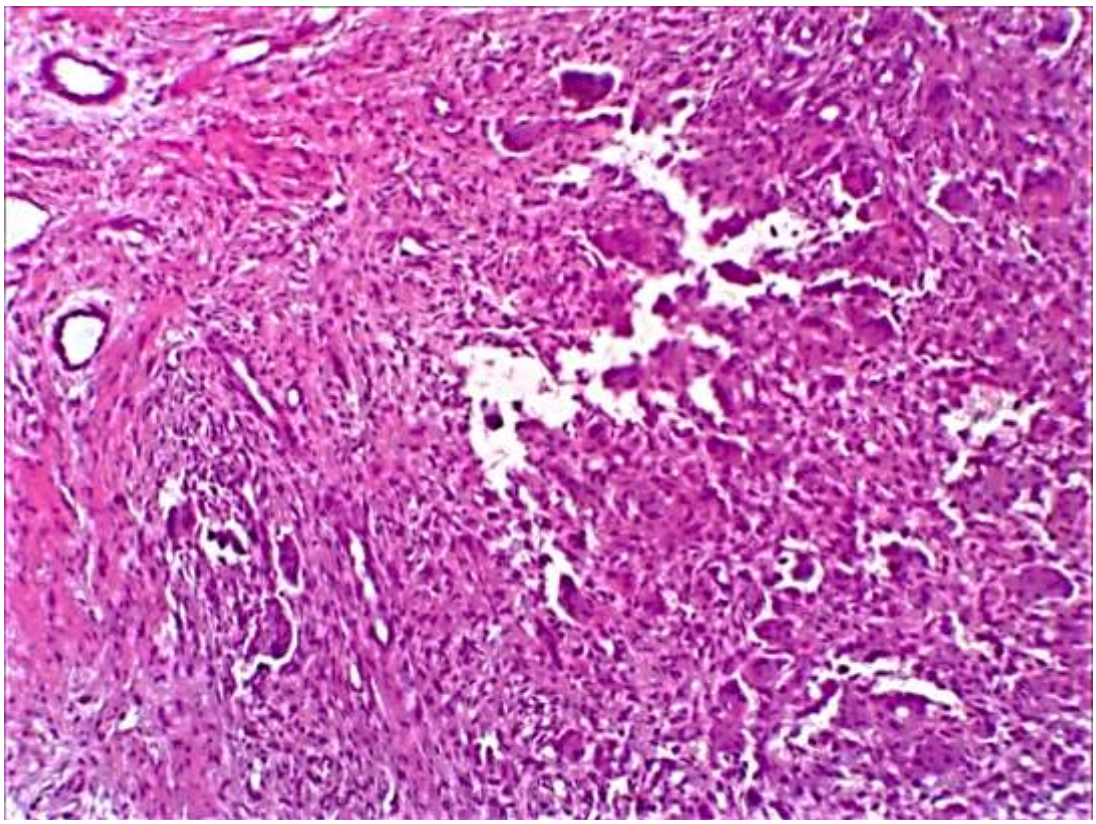

Figure (4): Clear zone (lacunae) around MNGCs in a case of PGCG (H&Ex100)

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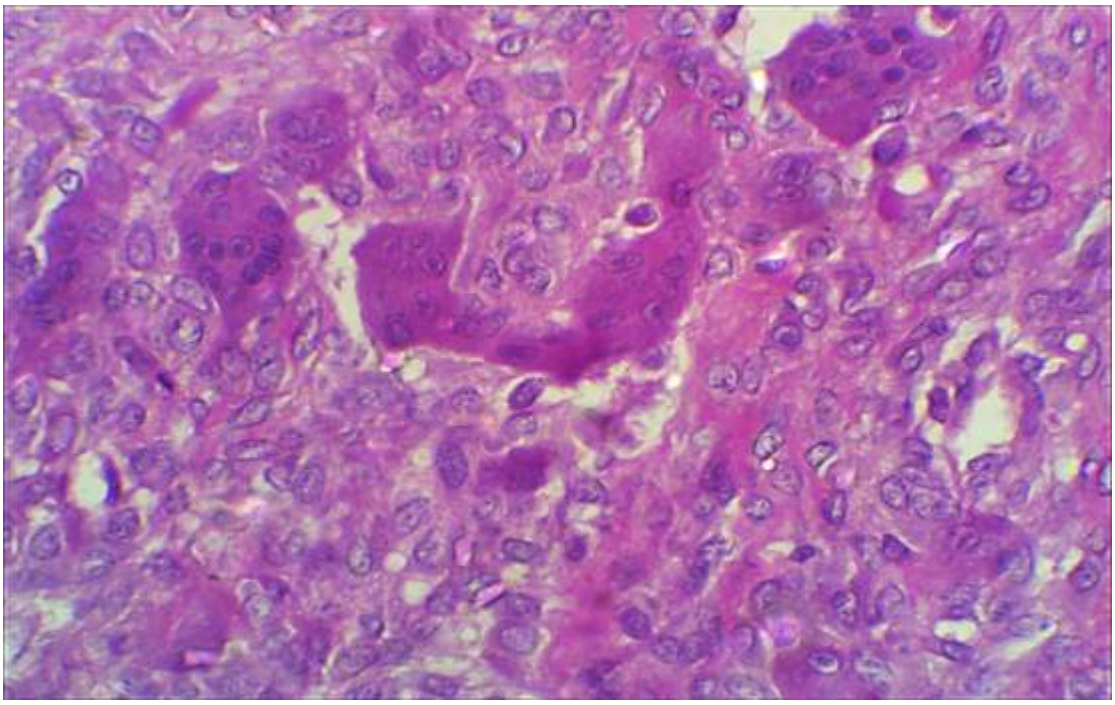

Figure (5): Photomicrograph showing partial cannibalistic cells in MNGCs (H&E x400)

2- Immunohistochemical Results

In the currently studied groups, the MNGCs showed a variable positive immunoreactivity localized in the cell membrane and the cytoplasm the MNGCs showed a moderate positive reaction that was presented in both the cell membrane and the cytoplasm of the MNGCs (figure 6,7,8). The stromal cells also encountered a positive reaction (figure 9).

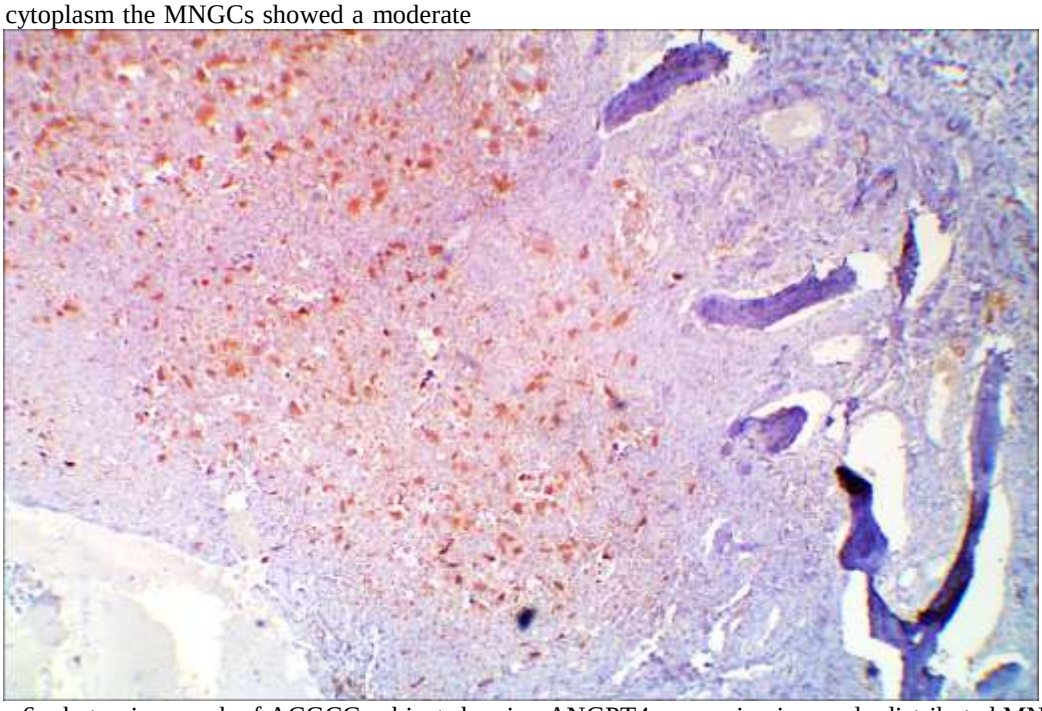

Figure 6: photomicrograph of ACGCG subject showing ANGPT4 expression in evenly distributed MNGCs (yellow arrows) with positive reactivity of bone (red arrows) (ABC-DAB x 40)

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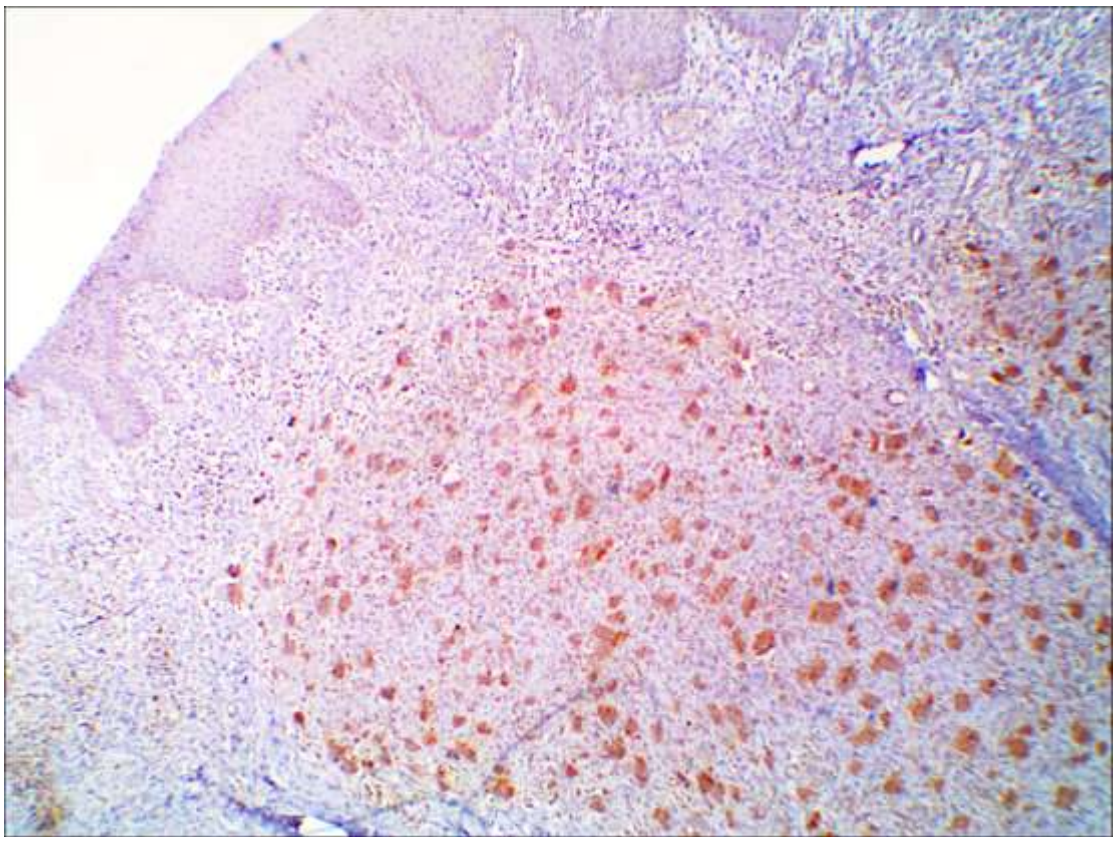

Figure 7:Photomicrograph of PGCG subject showing ANGPT4 positive reaction in MNGCs (ABC-DAB x 40x).

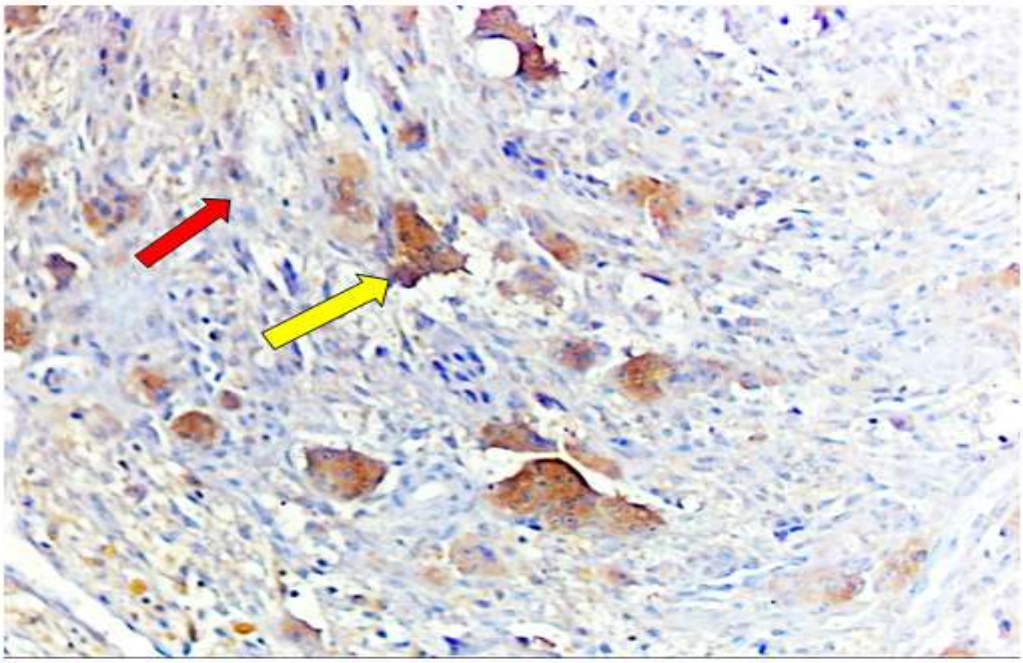

Figure 8: Higher magnification of the previous photomicrograph of the PGCG case showing ANGPT4 expression in MNGCs (yellow arrows), and stromal cells (red arrows) (ABC-DAB x 100)

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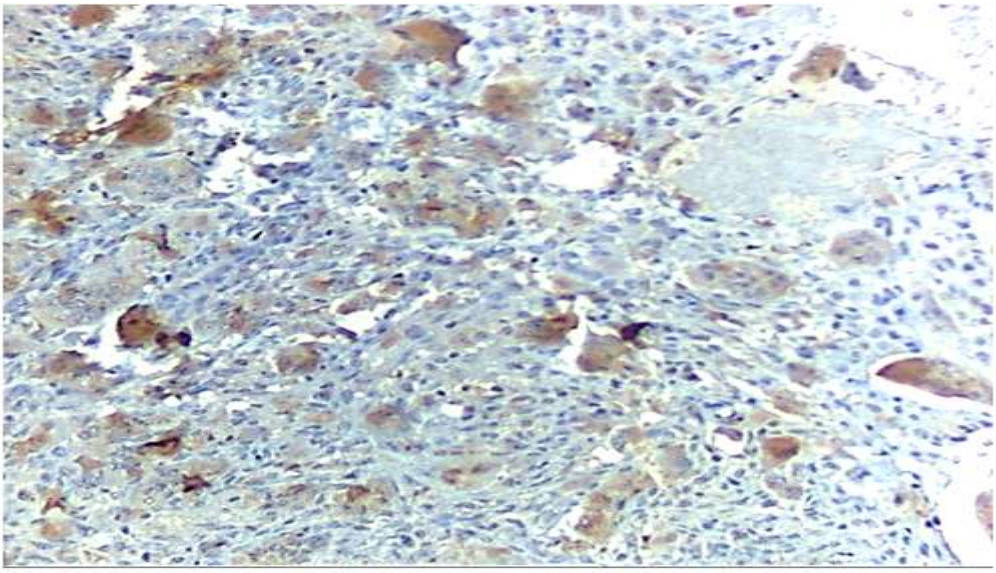

Figure 9: photomicrograph of CGCG showing ANGPT4 expression in MNGCs and positive reaction of stromal cells (ABC-DAB x 100)

IV. DISCUSSION:

Regarding age, the age of the studied cases ranged from 6 to 67 years. The mean age of the studied GCG groups showed variation among the studied groups where the highest mean was encountered in the PGCG group (40.3) and the lowest was among the ACGCG group (34.8), which agrees with (Sarode et al. 2017) and (Urs, Yaming, and Malhotra 2018) who stated that the lesion occurred mostly in young adults.

Regarding gender, a slight female tendency was encountered. This observation was in accordance with (Urs, Yaming, and Malhotra 2018), (Chrcanovic, Gomes, and Gomez 2018) and (Sadri et al. 2019).Predominant incidence in female suggests that both CGCG and PGCG could be under influence of ovarian hormones as mentioned by (Patil et al. 2018). But this in contrast to thesis of (Sarode et al. 2017) who stated that the incidence in males found to be equals females. The difference might be caused by different ethnicity or small sample size.

As regards the site, most of cases found to occur in mandible than maxilla which agrees with the results of (Sarode et al. 2017), (Chrcanovic, Gomes, and Gomez 2018) and (Sadri et al. 2019).This might be referred to that, the maxilla is known to have a significant blood flowwhich make it less prone to infection as discussed by Mohite, Motwani, and Assudani (2017).

Regarding pain, almost of cases of PGCG and NACGCG were asymptomatic which agrees with (Chrcanovic, Gomes, and Gomez 2018) and (Kudva et al. 2018).This might confirm their non-aggressive biological behavior. Moreover, most of the current aggressive CGCG cases have been reported with pain. This was in agreement with previous study of (Reham Mostafa, El-Serbeny, and El-Nagdy, n.d.).Thus, this mightindicate that aggressiveness of these cases.

Multinucleated giant cells are found in most oral lesions as a secondary component but in GCG lesions, they are important functioning cells. Distribution of MNGCs in specimens may be a good indicator to the behavior of the lesion. The uneven distribution may be indicator to the reactive nature of the lesion (Arumugam et al. 2023). Cellular cannibalism is engulfment of a small cell by another larger cell within its cytoplasm. This phenomena has been discussed as an indicator for aggressiveness of malignancies in breast, pulmonary and bladder cancers (Siddiqui et al. 2019)

In the present study The ANGPTL4 found marked cytoplasmic and membranous reaction of giant cells. Marked reaction has been shown in the aggressive type, non-aggressive type, then peripheral type respectively with marked significant differences between them. These finding can suggest that increase ANGPTL4 expression in the aggressive GCG lesions as indicating the aggressive behavior of these lesions and this might indicate high metabolic activity in CGCG cases than PGCG, likewise, in aggressive CGCG than non- aggressive cases.ANGPTL4 promotes cell proliferation,tumor progression and osteoclast differentiation. This was in agreement with (Li et al. 2017) and (Zhang et al. 2018).This

finding, inspite needing further investigation, however, it might clarify the more aggressiveness of the aggressive CGCG subgroup, in comparison with PGCG and non aggressive ones through the accompanied descending of the immunity

V. CONCLUSION:

The current work was conducted to highlight the relation of ANGPTL4 protein with GCGs. The study demonstrated that ANGPTL4 was moderate to strong reactions in CGCGs and low to moderate reaction in PGCGs. So, ANGPTL4 can detect the biological behavior ofthese lesions as it proves that the CGCGs are aggressive lesionsand PGCGs are non-aggressive lesions.

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