Review Article

Unravelling the role of immunohistochemistry in giant cell lesions of jaws: A systematic review

Shruti Gupta[1], Deepti Sharma[2], Anita Hooda[1], Vishal Kumar Sharma[3], Mala Kamboj[4]

Departments of [1]Oral Anatomy and [4]Oral Pathology, Post Graduate Institute of Dental Sciences, Rohtak, Haryana, [2]Department of Oral and Maxillofacial Pathology, Christian Dental College, Ludhiana, Punjab, [3]Department of Orthodontics, Desh Bhagat Dental College, Mandi Gobindgarh, Punjab, India

Abstract

Controversies exist in literature regarding nature, pathogenesis, and behaviour of giant cell lesions (GCLs) of jaws. Studies were attempted to solve these mysteries with immunohistochemical analysis, using various biological markers. Thus, the aim of this review is to appraise the role of immunohistochemistry (IHC) in evaluating the pathogenesis, cellular phenotype, nature, and behaviour of GCLs of jaws. PubMed, PubMed Central, and Clinical Key (Medline) databases were searched electronically irrespective of date of publication with assortment of several independent terms. Fifty-five articles that fulfilled the eligibility criteria were included in the review. Out of 55 included articles, 49 were associated with nature, pathogenesis, and behaviour and six articles were associated with treatment and outcome prediction. Although IHC solved some of the controversies associated with GCLs of jaws such as the osteoclastic phenotype of multinucleated giant cells, immunoexpression of proliferative markers does not distinct non-aggressive from aggressive central GCL but the nature, histogenesis, pathogenesis, and exact behaviour still remain debatable. With regard to formulation of treatment plan, immunohistochemical analysis revealed that expression of glucocorticoid and calcitonin receptors could act as a tool to decide the therapeutic strategy and aid in therapeutic adjustments according to evolution of the lesion.

Keywords: Giant cell lesions, granuloma, immunohistochemistry, jaws, pathogenesis

Address for correspondence: Dr. Shruti Gupta, H.No. 166, OLD P.L.A Sector, Hisar, Haryana, India.
E-mail: guptashruti.82@gmail.com

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INTRODUCTION

Wide spectrum of giant cell lesions (GCLs) occurs in the maxillofacial region with varied clinical manifestations and unpredictable biological course but unified by the ubiquitous presence of multinucleated giant cells (MGCs). The GCLs, such as central giant cell granuloma (CGCG), peripheral giant cell granuloma (PGCG), cherubism, aneurysmal bone cyst, giant cell tumor (GCT), and osteitis fibrosa cystica are associated with proliferation of fibroblasts, macrophages, and MGCs.[1,2] Terminologies central giant cell lesion (CGCL) and peripheral giant cell lesion (PGCL) of jaws are used for those lesions that occur centrally within the bone and peripherally in periodontal ligament and mucoperiosteum.[2-4] Despite having similar histological features, these lesions exhibit a wide spectrum of biological behaviour, from indolent and slow growing to rapidly progressing and destructive, reminiscent of GCT of long bones.[5] From their inception as reparative granuloma

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until date, many aspects of their histogenesis and biological behaviour remain unresolved.[6,7] PGCL of jaw is believed to be a reactive lesion, which could arise in response to a local irritating factor that shows low-recurrence rate.[8] The true nature of jaw CGCLs is vague and still debatable whether it has reactive, inflammatory, infectious, or neoplastic origin.[9,10] However, GCT of long bones is considered to be a benign locally aggressive osteolytic neoplasm.[5,11] This raises the question whether these lesions are separate entities or they represent a wide spectrum of same disease; which is still unanswered.[5,12] Many aspects of GCLs of jaws, including their histogenesis, phenotype of cellular component and their role in proliferation of these lesions, clinical and biological course, and prognosis still remain ambiguous. Therefore, there is an upsurge in the research work in the last few decades focusing on the evaluation of molecular markers, which may help in better understanding of behaviour and nature of these lesions, but the dilemma still exists.[13] Thus, there is a need to solve the mysteries surrounding these lesions so that correct diagnosis, molecular targets, and standardised treatment protocols could be established. This systematic review is designed to comprehend the role of immunohistochemistry (IHC) to appraise certain established facts as well as highlight controversial concepts regarding GCLs of jaws.

METHODOLOGY

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Eligibility criteria

Articles were included if they met all the following criteria: (a) Immunohistochemical studies on giant cell granulomas of jaws and (b) studies published in the English language and studies for which full text was available on internet. Review articles, case reports/case series, conference abstracts, duplicate articles, dissertations, abstract only articles, articles with data variability, articles in language other than English, articles for which full text was not available on internet, articles pertaining to any other lesions of jaws, studies in which molecular modalities other than IHC were performed, studies based on GCT of long bones alone, studies done on GCLs other than CGCL and PGCL of jaws, and studies not using human subjects/samples were excluded from the review.

Search strategy

The following databases were assessed: PubMed, PubMed Central, and Clinical Key (full-text articles and articles indexed in MEDLINE) until October 31, 2020. The search strategy included use of the following keywords: central giant cell granuloma jaws, peripheral giant cell granuloma jaws, giant cell granuloma jaws, reparative giant cell granuloma jaws, central giant cell lesion jaws, peripheral giant cell lesion jaws, giant cell lesion jaws, reparative giant cell lesion jaws in combination with terms 'immunohistochemistry or immunohistochemical' with Boolean operator 'and' between them. All articles that satisfied the eligibility criteria were included. The references for included articles were also searched for any studies not retrieved by the electronic search.

Article screening and eligibility evaluation

Titles and abstracts of all the articles were screened by two independent reviewers (Shruti Gupta and Deepti Sharma), and articles that did not meet the eligibility criteria were excluded. Then, the two authors proceeded with the eligibility evaluation by reading the full text of the articles. Disagreements were resolved first by discussion and then by consulting a third reviewer (Mala Kamboj) in a consensus meeting [Figure 1].

Data extraction

Data were extracted by one author (Shruti Gupta) and revised by a second author (Deepti Sharma) to warrant the integrity of contents. The following information was extracted: aim, study design, sample size, immunohistochemical marker studied, interpretation, and conclusion of the study.

RESULTS

Out of included 55 articles, 24 articles studied role of IHC in both PGCLs and CGCLs of jaws, followed by CGCLs of jaws (20), combined PGCLs, CGCLs of jaws, and GCT of long bones (6), PGCLs of jaws (3), and both CGCLs of jaws and GCT of long bones (2).

Nature of cellular components

Table 1[4,14-20] included the studies that were associated with nature of cellular components in GCLs of jaws. Majority of the studies were of the opinion that MGCs were osteoclastic in nature.

Pathogenesis and nature of GCLs of jaws

Twenty studies were mainly associated with pathogenesis and nature of GCLs of jaws [Table 2].[2-3,11,13,21-36] Studies suggested p63 and OCT-4 as the markers that could differentiate between GCT of long bones and GCLs of jaws.

Behaviour of GCLs of jaws

Twenty-one studies were mainly associated with behaviour of GCLs of jaws[Table 3].[5,8,37-55]

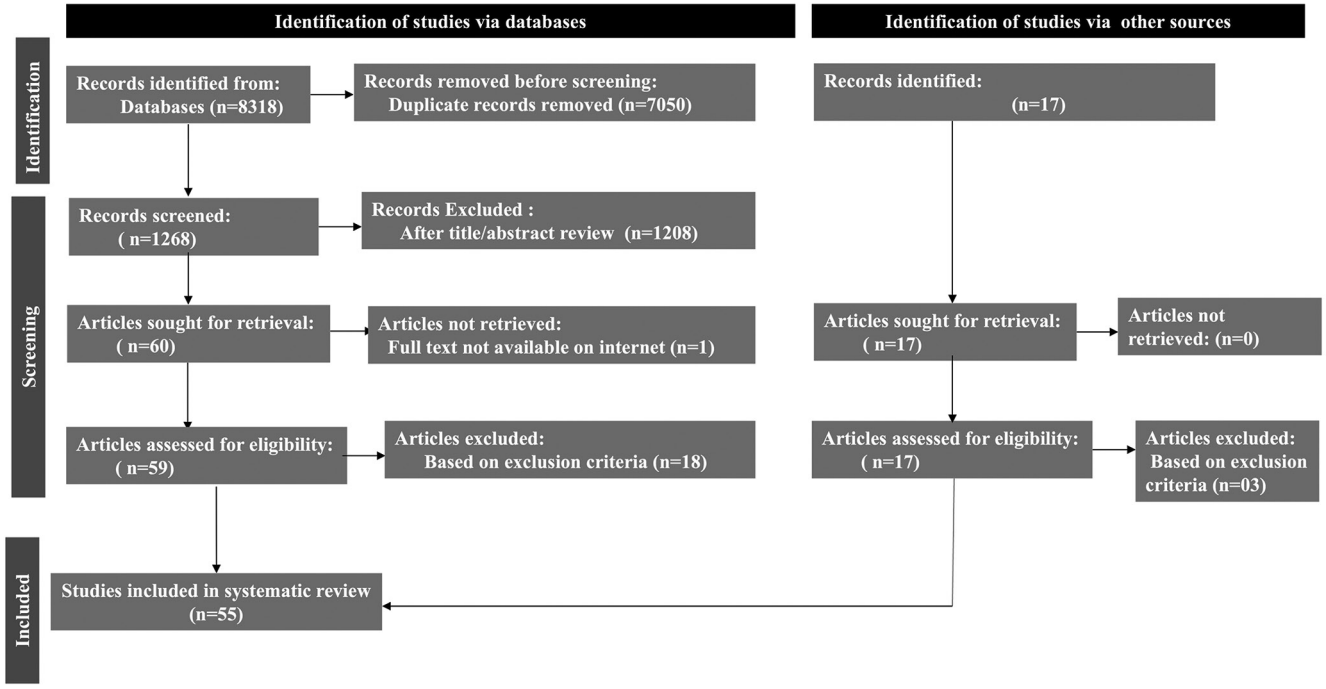

Figure 1: Flow chart depicting the search process for systematic review

Treatment of GCLs of jaws

Table 4[56-61] included the immunohistochemical studies that were related with management of jaw GCLs. Studies reported that glucocorticoids and calcitonin could be used in a non-surgical approach for treatment of CGCLs.

DISCUSSION

Literature reported that gnathic GCLs were well delineated from GCT of long bones as giant cell reparative granulomas. As the clinical behaviour of many of these lesions is inconsistent with a reparative reaction, the designation giant cell granuloma or the more noncommittal term giant cell lesion is most widely used today.[6]

Nature of PGCLs and CGCLs

Immunohistochemical markers have been used to ascertain the reactive potential of the peripheral lesions. de Matos *et al*.[39] and Naji *et al*.[28] reported that higher expression of TNF-α might be related to the reactive nature of these lesions where the inflammatory process contributes to greater release of inflammatory cytokines and increased angiogenesis. It is still uncertain whether PGCL is a discrete entity or peripheral variant of a CGCL.[5,10,32] The nature of CGCL is still obscure and as mentioned by Ahmed and Dunlap,[62] its reactive nature has recently been questioned because of its potential aggressive nature, bone destruction, and a high-recurrence rate of 11–35%. Some CGCLs demonstrate aggressive behaviour such as a neoplasm[10,48] and various speculations have ascertained that perhaps there is a reactive and a neoplastic form of CGCL.[2]

Contradictory facts are available in designating CGCL as proliferating vascular lesions. Vered *et al*.[23] have not supported true proliferative vascular nature of CGCL, whereas Sadri *et al*.[54] favoured the possible vascular-proliferative nature.

Nature of CGCLs and GCTs

The literature revealed a distinct delineation between GCT of the long bones and CGCL, the former being more aggressive and difficult to treat.[63] Some researchers reported that both CGCG and GCT represent two separate entities, whereas other workers believed them to be spectrum of same disease.[10,16] Some opined that GCT and CGCL are influenced by the age and site of occurrence in the patient.[2,6,11,63] However, other studies reported that they are two separate entities with different pathogenesis and OCT-4 and p63 immunostaining could distinguish them.[3,31] Currently, based on cytogenetic studies, distinct status is assigned to both as somatic mutations in the *H3F3A* gene are identified in GCTs but not in CGCGs.[49] Some authors suggested that true GCT of bone is rare in jaw, whereas others believe that it can occur in jawbones.[64,65] Therefore, it can be inferred that different hypothesis have been proposed, justified, and opposed from many years to describe the nature of jaw GCLs.

Table 1: Immunohistochemical studies mainly associated with nature of cellular components of GCLs of jaws

Author	Group	Sample Size			IHC Marker studied	Interpretation	Conclusion
		PGCL	CGCL	GCT			
Bonetti *et al*. [14]	PGCG	9	–	–	1. Lysozyme 2. HAM 56 3. MAC 387 4. MB1	GCs were lysozyme, MAC 387, HAM 58 negative but MBl positive.	GCs might be true osteoclasts.
O'Malley *et al*.[15]	CGCG	–	16 A & 12 NA	–	1. CD34 2. CD68 3. factor XIIIa, 4. α-smooth muscle actin 5. Prolyl 4-hydroxylase 6. Ki-67 7. p53	1. α-smooth muscle actin positive in CGCG. 2. CD68 expression could not be related to behaviour of lesion. 3. Ki-67 and p53 did not differentiate between A-and NA-CGCG. 4. Rare p53 gene positivity in CGCG.	1. CGCGs are primarily fibroblastic (and myofibroblastic) tumors in which macrophages appear to play a secondary role. 2. Tumor cells do not show differentiation toward endothelial cells or macrophage-related dendrocytes.
Moussa *et al*.[16]	PGCG CGCG GCT	10	10	12	1. p53	1. Significantly high intensity of p53 staining of the MSCs in PGCG versus CGCG and GCT. 2. Significantly higher percentage of positive nuclei/GC in GCT in comparison to CGCG and PGCG.	Positive expression of p53 in both MGCs and stromal cells suggested that MGCs might be formed by the fusion of MSCs.
do Socorro Aragão *etal*.[17]	CGCG GCT	–	8	7	1. CD 68 2. Fibronectin 3. Tenascin	1. MGCs and many MSCs in GCLs showed positivity for CD68. 2. Fibronectin and tenascin not significant to differentiate between two lesions.	1. MGCs and MSCs had histiocyte/macrophage origin. 2. These two lesions are sometimes indistinguishable.
Fanourakis *et al*.[18]	PGCG	22	–	–	1. RANKL 2. OPG	1. OPG and RANKL expression in stromal cells was consistent with their purported osteoblastic lineage. 2. Round MSCs expressed RANKL and OPG.	Expression of OPG and RANKL in PGCG of the jaw supported the osteoclastic nature of GCs.
Houpis *et al*.[19]	PGCG CGCG	20	20	–	1. PTHrP 2. PTHR1 3. MSX1	1. Expression of PTHrP, PTHR1 and MSX1 in type I MGCs was consistent with their osteoclastic phenotype. 2. Statistically significant difference was seen between CGCG and PGCG regarding the expression of PTHrP and PTHR1 in type II MGCs. 3. PTHrP and PTHR1 positive MSCs with vesicular nuclei represents osteoclast precursor cells. 4. Presence of MSX1 expression in MSCs showed their proliferative capacity.	1. Due to role of PTHrP and PTHR1 in osteoclastogenesis, study emphasised on exploring PTHrP/PTHR1 pathway as therapeutic target. 2. In CGCG most type II MGCs have osteoclastic phenotype but in PGCG, they could be reactive GCs. 3. GCLs of the jaws might originate from the periosteum or the endosteum of the jawbones or the periodontal ligament.
Torabinia *et al*.[4]	CGCG PGCG	20	20	–	1. CD68 2. TRAP	In both PGCG and CGCG, GCs and a group of MSCs showed positivity for TRAP and CD68 antibody.	1. GCs are osteoclast-like cells; however, their origin is either macrophagic or monocytic. 2. Fusion of MSCs results in formation of GCs.
Mohtasham *et al*.[20]	PGCG CGCG	37	37	–	1. MMP-2 2. OPN	1. Significantly higher expression of MMP-2 and OPN in CGCG was seen as compared to PGCG. 2. MMP-2 expression in stromal cells and GCs in CGCG indicated the role of these cells in destroying the bone matrix. 3. Statistically non-significant higher expression of OPN was observed in MGCs in comparison to MSCs in both PGCG and CGCG.	1. The expression of OPN in GCs supports the osteolcastic nature of these cells. 2. OPN and MMP-2 expression in MSCs suggest the monocyte-macrophage origin of these cells. 3. Differences in biological behaviours of these lesions were associated with the level of expression of osteolytic and proteolytic marker.

A=Aggressive, CGCL=Central giant cell lesion, CGCG=Central Giant cell granuloma, GC=Giant cells, GCT=Giant cell tumor, GCL=Giant cell lesions, MGC=Multinucleated giant cells, MSC=Mononucleated stromal cells, NA=Non-aggressive, PGCG=Peripheral giant cell granuloma, PGCL=Peripheral giant cell lesion, OPN=Osteopontin, OPG=Osteoprotegrin

Nature of MGCs and Mononucleated stromal cells (MSCs) in jaw GCLs

The concept was put forward initially that MGCs might arise from the fusion of histiocytes, fibroblast, myofibroblasts, endothelial cells, MSCs, or osteoclasts progenitor cells.[43,56] Majority favour their formation by the fusion of precursors that have monocyte/macrophage lineage.[1,5,17,43,45,66] Candido-Soares[67] based on their findings

Table 2: Immunohistochemical studies mainly associated with pathogenesis and nature of GCLs of jaws

Author	Group	Sample Size			IHC Marker studied	Interpretation	Conclusion
		PGCL	CGCL	GCT			
Whitaker and Bouquot[21]	CGCL	–	10	–	1. ERS proteins 2. PRS proteins	Stromal cells and MGCs were negative for ERS/PRS proteins.	CGCL was not under the direct influence of these hormones.
Whitaker and Bouquot[22]	PGCL	10	–	–	1. ERS proteins 2. PRS proteins	1. Five out of 10 ERS positive. 2. Negative PRS in all cases.	PGCL partially under hormonal influence
de Souza *et al*.[11]	GCT CGCG	–	14	9	1. p53 2. MDM2 3.Ki-67 4. PCNA	1. p53 negative and MDM2 positive in both GCT and CGCG. 2. CGCG showed higher percentage of Ki-67 and PCNA-positive cells compared to GCT. 3. MGCs in both the lesions were negative for Ki-67 and PCNA.	Inactivation of p53 by MDM2 expression may be involved in the pathogenesis of GCLs of the jaws and long bones.
Vered *et al*.[23]	CGCG	–	41	–	1. VEGF 2. bFGF	CGCG with more VEGF- and bFGF-producing cells exhibited more aggressive biologic behaviour.	1. CGCG is not a true proliferative vascular lesion. 2. Attractive target for anti-VEGF treatment.
Matos *et al*.[24]	CGCL PGCL	20	20	–	1. VEGF 2. MMP-9 3. vWF	1. CGCL showed higher percentage of MMP-9 immunoreactive cells than PGCL. 2. In spite of higher VEGF expression in CGCL, a negative correlation was observed between MVC and VEGF expression.	1. In CGCL, VEGF and MMP-9 might play an important role in the osteoclastogenesis process and consequently to bone resorption. 2. Greater vascularization in PGCL might be associated with inflammatory reactive nature of these lesions.
Kader *et al*.[2]	PGCG CGCG GCT	16	15	17	1. PCNA 2. p53	1. p53 and PCNA expression was comparable between GCLs and GCT. 2. High p53 expression might be associated with a more aggressive clinical behaviour.	1. Both the conditions may act as one disease entity with a spectrum of clinical behaviour. 2. CGCG of jaws may be considered as low-grade tumor.
Nogueira *et al*.[13]	CGCL	–	18 (9 A and 9 NA)	–	COX-2	Both MSCs and MGCs in only three cases (2 A and 1 NA) revealed COX-2 cytoplasmic reactivity.	COX-2 does not participate in the early etiopathogenesis of CGCL.
Falci *et al*.[25]	CGCL PGCL	14	13	–	1. FASN 2. CD34 3. CD105 4. D2-40	1. FASN-positive MGCs and MSCs were observed in all cases without any significant difference between CGCL and PGCGL with greater number of MGCs showing immunopositivity than MSCs. 2. Uniform positivity was observed for CD34 in all vascular structures in both lesions. Almost all cases exhibited CD105-positive vessels, whereas only 78% and 69% of the PGCL and CGCL, respectively, showed D2-40-positive vessels. 3. A significant correlation was observed between FASN-positive MSCs and MVA–CD105 in both studied lesions.	Greater MVD-CD34 and greater MVA-CD34, CD105, and D2-40, in PGCL rather than in CGCL, might be associated with a reactive inflammatory process.
Hallikeri *et al*.[26]	CGCG PGCG	40	40	–	1. CD34 2. CD68	1.CGCG showed statistically significant greater number of CD34-positive microvessels and more mean MVD in comparison to PGCG. 2. The macrophages were found to be significantly more in CGCG.	Angiogenesis could affect the architecture or pattern of growth in GCLs of jaw as suggested by mean MVD.
Merza[27]	CGCG PGCG GCT	15	15	15	1. WWOX 2. Ki-67	1. The stromal cells of CGCG, PGCG, and GCT revealed positive Ki67 immunostaining. PGCG showed high proliferative expression score compared to CGCG and GCT. 2. WWOX could not be used to delineate between the GCLs of the jaws and GCT of the long bones.	Similarities in the expression of WWOX and Ki-67 in CGCG, PGCG of jaws, and GCT of long bones with non-significant correlation between them suggested that these lesions are spectrum of disease but with different clinical behaviour.

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Table 2: Contd...

Author	Group	Sample Size			IHC Marker studied	Interpretation	Conclusion
		PGCL	CGCL	GCT			
Naji *et al*.[28]	PGCG CGCG GCT	20	20	20	1. TNF-α 2. IL-6 3. VEGF	1. A direct correlation between the stromal cells and MGCs in relation to the expression of TNF-α was observed. 2. With regard to TNF-α, a highly significant difference between PGCG and GCT and between PGCG and CGCG was seen. 3. The comparison among CGCG, PGCG, and GCT revealed no significant difference regarding the expression of IL-6 by MGCs.	1. TNF-α, IL-6, and VEGF are useful in assessing osteoclastogenesis. 2. Comparable biological activity of TNF-α, IL-6, and VEGF between CGCG and GCT supports the hypothesis that these two lesions are same entity and have same biological behaviour. 3. High levels of VEGF-producing cells in CGCG would be related to a more aggressive biological behaviour.
Shahsavari *et al*.[29]	CGCG PGCG	15	15	–	1.Ki67 2. p27	1. No statistically significant difference in expression of both Ki67 and p27 between CGCG and PGCG. 2. About 86.7% of PGCG and 60% of CGCG showed weak expression of p27. 3. In CGCG, a negative correlation was observed between expression of Ki67 and p27, whereas no correlation was found between studied markers in PGCG.	Non-tumoral and reactive behaviour of PGCG and CGCG has been confirmed.
Vasconcelos *et al*.[30]	PGCL CGCL	20	A-20 NA-20	–	1. GLUT-1, 2. GLUT-3, 3. M-CSF	1. MSCs showed GLUT-3 expression in all cases but 73.3% of MGCs did not show GLUT-3 expression. 2. A-CGCL showed maximum GLUT-1-positive MSCs (90%) followed by NA-CGCL (85%) and PGCL (55%). 3. Expression of M-CSF was constant in most cases (>75% of MSCs and MGCs). 4. MSCs showed stronger staining for the studied proteins especially in A-CGCL.	1. It was postulated that GLUT-1, GLUT-3, and M-CSF could play a role in the pathogenesis of the GCGs of jaws. 2. In comparison to MGCs, MSCs cells were strongly associated with the pathogenesis of CGCG and PGCG. 3. MGCs would most likely derive from the cytoplasmic fusion of several MSCs. 4. Low intensity of staining for GLUT-1 suggested that GCLs of jaw generally showed a benign behaviour.
Hosur *et al*.[31]	CGCG	–	10	–	1. p63 2. RANK-RANKL (Selected Cases)	1. p63 was not expressed in CGCG. 2. MSCs and GCs showed strong and diffuse positivity for RANK and RANKL.	1. Study confirms the non-neoplastic nature of CGCG. 2. p63 can be used as marker to distinguish CGCG and GCT. 3. GCs were osteoclastic in nature.
Martini *et al*. [32]	CGCL PGCL	20	20	-	1.RANKL 2. OPG	1. Study revealed an intense immunoexpression of RANKL in CGCL than in PGCL and also a higher expression of RANKL and OPG in recurrent lesions. 2. No difference in OPG expression between both studied lesions. 3. Positive correlation was observed between the RANKL to OPG ratio in both CGCL and PGCL.	The difference in clinical behaviour between CGCL and PGCL and their pathogenesis is explained via higher RANKL expression and a greater number of nuclei in MGCs in CGCL.
Atarbashi Moghadam and Ghorbanpour [33]	CGCG	–	A-16 NA-16	–	1. Cyclin D1	1. Cyclin D1 might play a role in the production of GCs. 2. Significantly higher mean percentage of positive MGCs in comparison to positive MSCs was observed. 3. No significant difference was seen in cyclin D1 expression between MGCs and MSCs of two groups.	1. Overexpression of cyclin D1 is implicated in the pathogenesis of the CGCGs. 2. Cyclin D1 could not be used as a marker for identifying the clinical behaviour of these lesions.
Saghravanian *et al*.[34]	CGCG PGCG	36	36		1. VEGF 2. Tryptase	1. Even though only MGCs showed statistically significant difference in VEGF expression between studied	1. The findings of the study may explain the different pathogenesis of two lesions, regardless of

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Table 2: Contd...

Author	Group	Sample Size			IHC Marker studied	Interpretation	Conclusion
		PGCL	CGCL	GCT			
				–		groups, increased immunoreactivity was seen in both MSCs and MGCs in CGCG. 2. Mean vessel count investigated by VEGF was higher in CGCG. 3. PGCG showed a greater number of mast cells compared to CGCG.	the similarity in histopathologic features 2. In CGCG, higher overall expression of VEGF might lead to increased vascularity as well as more destructive nature.
Melo-Muniz *et al*.[35]	CGCG	–	NA-12 A-11	–	1. SHH 2. GLI1 3. cyclin D1 4. SMA	1. The involvement of components of the HH-signaling pathway (SHH and GLI1), cyclin D1, and myofibroblasts was revealed in CGCG. 2. A significant positive correlation was observed between Cyclin D1 and GLI1 in A-CGCG. 3. In comparison to other proteins, higher expression of SMA was observed in all cases.	1. HH-signaling pathway, myofibroblastic differentiation, and cyclin D1 expression could not be related with aggressiveness of the lesion. 2. Activation of the HH-signaling pathway might contribute to the development and maturation process of CGCG and could be a potential therapeutic target. 3. Myofibroblasts were main supporting component of CGCG.
Bodhankar *et al*.[3]	PGCG CGCG GCT	10	10	10	1. OCT-4 2. SOX-2	1. In GCT, positive expression of OCT-4 was observed in the nuclei of the MSCs but not in GCs. However, both MSCs and MGCs were negative for SOX-2. 2. OCT-4 and SOX-2 were negative in CGCG and PGCG.	1. OCT-4 could be used as marker to differentiate GCT from CGCG and PGCG but it cannot differentiate between CGCG and PGCG. 2.Three conditions are separate entities.
Melo-Muniz *et al*.[36]	CGCG		A-11 NA-12		1. CD68 2. CD163 3. CD34 4. CD105 5. D2-40 6. p63 7. Ki-67	1. CD68 and CD163 expression revealed a positive correlation in CGCG regardless of the clinical variant. 2. No significant differences were observed in the expression of the vascular markers between NA- and A-CGCG. 3. A negative correlation between the expression of CD105 and CD68 in A-CGCG was seen. 4. No correlation was found between the macrophage markers and D2-40 in spite of positive correlation between D2-40 and CD34. 5. Lack of expression of Ki-67 does not affect the aggressive clinical behaviour of CGCG. 6. p63 does not seem to participate in cell proliferation in CGCG.	1. Regardless of the lack of correlation between vascular proteins and macrophage markers, macrophages and angiogenesis contribute to the development and maintenance of the lesion and in addition, lymphangiogenesis also appears to influence this process. 2. Immunoexpression of the markers used in this study is unable to differentiate the A from the NA variant. 3. Development of CGCG was strongly influenced by the vascular proteins CD34 and D2-40 unlike CD105.

A=Aggressive, CGCL=Central giant cell lesion, CGCG=Central Giant cell granuloma, ERS=Estrogen receptor, FASN=Fatty Acid Synthase, GC=Giant cells, GCT=Giant cell tumor, GCL=Giant cell lesions, MVA=Microvessel area, MGC=Multinucleated giant cells, MSC=Mononucleated stromal cells, MVC=Microvessel count, MVD=Microvessel density, NA=Non-aggressive, PRS=Progesterone Receptor, PGCG=Peripheral giant cell granuloma, PGCL=Peripheral giant cell lesion, OPG =Osteoprotegrin, COX-2=Cyclooxygenase 2

suggested that secreted osteoclastogenic factor of activated T-cells (SOFAT) could act as a putative marker of osteoclasts, which can differentiate osteoclasts from multinucleated macrophages and confirmed that MGCs in CGCLs and PGCLs of jaw have an osteoclastic phenotype. Controversy still exists regarding the nature of MSCs as it is said to have fibroblast, myofibroblast, macrophage, or endothelial origin.[18,50] Vered *et al*.[37] suggested that the MSCs in CGCLs undergo a dynamic process of transdifferentiation rather than existing in a constant state. Based on these collaborative findings, it could be said that although the exact origin for MGCs and MSCs is still debatable but almost all researchers agreed on the fact that MGCs have osteoclastic phenotype.

Role of MGCs and MSCs in GCLs

MSCs represent the proliferating compartment and are responsible for the growth of GCLs of jaws,[5,15,52] whereas MGCs are considered as reactive component only, which do not contribute to biological behaviour of these lesions.[5,11,49] However, Itonaga *et al*.[66] reported that osteoclast-like MGCs in these lesions produce the osteolysis and are associated with their growth, whereas EI-Attar *et al*.[45]

Table 3: Immunohistochemical studies mainly associated with behaviour of GCLs of jaws

Author	Group	Sample Size			IHC Marker studied	Interpretation	Conclusion
		PGCL	CGCL	GCT			
Vered *et al*.[37]	CGCG	–	A - 17 NA - 24	–	1. Alpha smooth muscle actin.	No significant difference between the two variants with regard to density of stromal myofibroblasts.	A and NA subtypes indistinguishable histologically.
Tobón-Arroyave *et al*.[38]	CGCLs	–	A - 30 NA - 12	–	1. MMP-1 2. MMP-9	Staining intensity and number of reactive MGCs and histiocytic MSCs vary depending on the aggressiveness of the lesion.	1. Differences in immunoreactivity of MMP-1 and MMP-9 proteolytic enzymes may underlie the distinct clinical behaviour. 2. CGCLs and GCTs of bone represent a spectrum of the same disease.
de Matos *et al*.[39]	CGCL PGCL	20	20	–	1. TNF-α 2. TGF- β	1. Higher expression of TNF-α in PGCL is consistent with the reactive nature of PGCL. 2. Significantly lower expression of TGF-β was observed in PGCL when compared to CGCL.	The coordinated interactions between TGF-β and TNF-α may be vital for osteoclastogenesis and bone resorption in CGCL.
Papanicolaou *et al*. [40]	PGCG CGCG	40	40	–	1. TNF-α 2. IL-6 3. IL-1β	1. All lesions expressed cytokines TNF-α, IL-6, and IL-1β. 2. The significantly increased expression of IL-6 and TNF-α and decreased expression of IL-1β by the spindle-shaped cells and increased expression of IL-1β by the MGCs was shown by CGCG in comparison to PGCG .	The trio of osteoclastogenic cytokines might have a role in the growth process of both extraosseous and intraosseous GCLs supporting similar growth potential for both.
Peacock *et al*. [41]	GCLs of jaws (CGCG)	–	A - 8 NA - 8	–	1. VEGF, 2. bFGF 3. CD31 4. CD34	1. Increased expression of VEGF and bFGF within both MGCs and mononuclear fibroblastic stroma was seen in the aggressive lesions. 2. Increased vascularity was quantified by reactivity to CD31 and CD34.	1. The protein markers of angiogenesis and endothelial proteins help to predict clinical behaviour. 2. GCLs of jaws are proliferative vascular lesion.
Khiavi *et al*. [42]	CGCG PGCG	30	30	–	1. Src protein	1. A significant correlation between Src expression and SID score was seen in both lesions. 2. Difference for both Src expression and SID score between PGCG and CGCG showed no statistical significance.	1. A role of Src (an osteoclastic factor) in resorptive activity of the MGCs in both PGCG and CGCGs of the jaws was suggested. 2. Src expression was not related to clinical behaviour of the lesions. 3. PGCG was considered as peripheral variant of CGCG.
Varsha *et al*. [43]	PGCG CGCG	20	20	–	1. CD34 2. CD68	1. Both MGCs and MSCs negative for CD34. 2. CGCG showed more CD68 expression in comparison to PGCG. 3. In both PGCG and CGCG, cytoplasm of MGCs and few of the stromal cells showed moderate-to-intense CD68 staining.	1. CD68 immunoreactivity may underlie the distinct clinical behaviour. 2. MGCs in both PGCG and CGCG originated from the fusion of stromal macrophages.
Kujan *et al*. [5]	PGCG CGCG GCT	28	26	6	1. Ki-67 2. p53 3. alpha-1-antichymotrypsin 4. CD68 5. Vimentin 6. alpha-smooth muscle actin	1. MSCs were positive for vimentin however, GCs showed negative staining. 2. In CGCG, PGCG, and GCT, myofibroblastic differentiation of many stromal fibroblasts was revealed by α-smooth muscle actin. 3. Both GCs and MSCs showed CD68 and alpha-1-antichymotrypsin immunoreactivity. 4. p53 expression was absent in all lesions. 5. The percentage of Ki-67-positive MSCs was significantly higher in	1. Authors suggested the same histogenesis of PGCG, CGCG, and GCT. 2. There was no correlation between the immunohistochemical markers and recurrence. 3. Aggressiveness of the lesions was attributed to the biological activity of MSCs, both histiocytic and myofibroblastic. 4. PGCG, CGCG, and GCT are different variants for the same disease. 5. GCs and MSCs have macrophages or their precursors as cell of origin.

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Table 3: Contd...

Author	Group	Sample Size			IHC Marker studied	Interpretation	Conclusion
		PGCL	CGCL	GCT			
						PGCG in comparison to CGCG and GCT. 6. GCs in all the studied cases except one case of PGCG showed negative immunoreactivity for Ki-67.	
Tobon-Arroyave *et al*. [44]	CGCL PGCL	23	45 (A – 32; NA - 13)	–	1. NF-kB 2. inhibitory subunits IkBα/IkBβ	Increase in nuclear activation of NF-kB and loss of IkBα might point towards proliferative activity and stimulation of distinct cellular components in the lesion that could lead to different extent of aggressive behaviour.	Expression of NF-kB, higher NF-kB to inhibitors average ratio, and decreased IkBα SID score could act as valuable parameters for predicting behaviour of CGCLs.
El-Attar and Wahaba[45]	PGCG CGCG	15	18 (A – 8; NA - 10)	–	1. Ki-67 2. CD31 3. CD68 4. p53	1. PGCG showed higher expression of Ki-67 than NA-CGCG. 2. Both GCs and MSCs in A-CGCG showed higher expression of Ki-67 compared to NA-CGCGs. 3. PGCG showed significantly higher expression of CD31 than CGCG. 4. A-CGCG expressed higher levels of p53. Both MGCs and stromal cells expressed p53 in A-type, whereas only MGCs expressed p53 in NA-type. 5. PGCG did not show p53 expression.	1. CD31 and CD68 expression cannot be used to distinguish between A and NA lesions. 2. Higher p53 expression could be used as a marker for aggressive behaviour of CGCG. 3. Both GCs and MSCs are involved in proliferative activity of these lesions. 4. Both PGCG and CGCG had the same origin. 5. GCs and some of the stromal cells were of histiocyte macrophage origin.
Farhadi *et al*.[46]	CGCG PGCG	20	20	–	1. VEGF	CGCG showed higher VEGF expression in comparison to PGCG with a statistically significant correlation between the two.	Higher concentrations of mast cells in CGCG than PGCG might lead to more aggressive clinical behaviour via vascular proliferation and angiogenesis.
Kumar *et al*.[8]	CGCG PGCG	20	20	–	1. CD34 2. CD68	1. Higher MVD in CGCG compared to PGCG. 2. CGCG had higher number of macrophages compared to PGCG. 3. An insignificant correlation between MVD and macrophage index was found among these lesions.	1. Macrophages had an important role in angiogenesis and angiogenesis may have a role in clinical behaviour therefore macrophages play an important role in proliferation of granulomas. 2. CGCG was more aggressive lesion than PGCG.
Zargaran *et al*.[47]	PGCG CGCG	20	20	–	1. Cathepsin D	Expression of Cathepsin D in GCs in PGCG and CGCG confirmed the osteoclastic nature of GCs.	More aggressive behaviour of CGCG can be explained based on higher expression of Cathepsin D in CGCG compared to PGCG.
Atarbashi Moghadam and Ghorbanpour[48]	CGCG	–	A - 16 NA - 16	–	1. CD34	A-CGCG showed higher average number of CD34 stained vessels than NA-type but this difference was not statistically significant.	Clinical behaviour of CGCGs cannot be recognised by CD34 protein.
Kahn *et al*.[49]	CGCG		67 (A – 36; NA - 31)		1. CSF-1R 2. CD68 3. CD163 4. NF-kB	1. Higher expression of CSF-1R (CD115) in NA-CGCG was seen. 2. There was a strong correlation between CD163-GC and NF-kB–GC within NA-CGCGs. 3. Higher expression of CD163 by MGCs was observed in NA-CGCG.	1. High expression of CD163-GC and CSF-1R (CD115)-MSCs, as well as increasing age, could serve as significant predictors of the NA variant of CGCGs. 2. CD163 positivity in GCs depicted macrophage lineage.
Sargolzaei *et al*.[50]	PGCG CGCG	19	22 (A – 10; NA - 12)	–	1. CD68 2. factor VIII-RA	1. CD68 expression was observed in almost 100% of MGCs as well as a small part of MSCs in PGCG, A-, and NA-CGCG. 2. MSCs played an important role in formation of MGCs by fusion.	1. High-intensity score and overexpression of CD68 in MSCs and the high-intensity score of factor VIII-RA in endothelial cells symbolise less aggressive behaviour in CGCG. 2. Some of the cellular components were histiocyte/macrophage in origin.
Zargaran *et al*.[51]	CGCG PGCG	30	30	–	1. CD105	1. Angiogenesis was found to be slightly higher in PGCG than CGCG. 2. No significant difference between	1. The study showed neovascularization in PGCG and CGCG. 2. Clinical behaviour of PGCG and

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Table 3: Contd...

Author	Group	Sample Size			IHC Marker studied	Interpretation	Conclusion
		PGCL	CGCL	GCT			
						both groups with regard to angiogenic potential.	CGCG is independent of number of vessels and angiogenesis.
Aksakalli[52]	PGCG CGCG	20	20	–	1. Ki-67, 2. OPN 3. integrin α_v	1. PGCG showed higher Ki-67 expression in MSCs compared to CGCG. 2. CGCG showed significantly higher expression of OPN in MSCs in comparison to PGCG but MGCs of both groups showed no significant difference with regard to OPN immunostaining. 3. MSCs of CGCG exhibited increased number of integrin α_v-positive cells in comparison to PGCG. 4. Both lesions showed similar expression of OPN, integrin α_v, and Ki-67 in MGCs.	1. Higher expression of OPN and integrin α_v might explain the more aggressive clinical behaviour of CGCG in comparison to PGCG. 2. MGCs do not have any role in the biological behaviour of these lesions.
Razavi and Yahyaabadi[53]	CGCG	–	A - 25 NA - 25	–	1. CD31 2. Ki-67	A-CGCG showed higher expression of Ki67 and CD31 in comparison to NA-CGCG.	Number of blood vessels and proliferation of fibroendothelial cells could be used as a reliable histopathological parameter to envisage the clinical behaviour of CGCG.
Sadri *et al*.[54]	PGCG CGCG	18	19	–	1. CD34 2. CD31	MVD assessed by both markers was significantly higher in CGCG as compared to PGCG.	1. Varied vasculature could be responsible for difference in biological behaviour of these lesions. 2. CGCG may be a vascular-proliferative lesion.
Mourad *et al*.[55]	PGCG CGCG	10	15 (NA - 8; A - 7)	–	1. VEGF	1. Increased staining of VEGF was observed in peripheral areas of PGCG. 2. A-CGCG showed high VEGF staining of MGCs and stroma. 3. PGCG showed lower expression of VEGF compared to CGCG.	GCLs with stronger VEGF expression have higher aggressive clinical behaviour.

A=Aggressive, CGCL=Central giant cell lesion, CGCG=Central Giant cell granuloma, GC=Giant cells, GCT=Giant cell tumor, GCL=Giant cell lesions, MGC=Multinucleated giant cells, MSC=Mononucleated stromal cells, MVD=Microvessel density, NA=Non-aggressive, PGCG=Peripheral giant cell granuloma, PGCL=Peripheral giant cell lesion, SID=Staining Intensity Distribution, OPN=Osteopontin

reported that both MGCs and MSCs are actively involved in the proliferation of these lesions.

Behaviour of GCLs

GCLs of jaws and GCT of long bones show a wide array of biological behaviour from relatively indolent and slow growing to rapidly growing and destructive.[5] Studies attempted to explicate their behaviour with the help of variety of biological markers (proliferative, angiogenic, and osteotropic markers) but have not identified one that can reliably describe their behaviour or differentiate aggressive from non-aggressive CGCL.[33,36]

The proliferative activity of any lesion can be determined by its growth rate.[45] Souza *et al*.[68] reported that innocuous-appearing PGCL showed increased proliferative activity and growth rate in comparison to CGCL that could be attributed to the existence of a secondary inflammatory infiltrate in the former lesion. de Souza opined in 1999 that CGCG showed higher proliferative activity in comparison to GCT.[11] These markers do not differentiate between aggressive and non-aggressive CGCL.[15,37]

Additional immune markers have been used to determine the behaviour of these lesions. Khiavi *et al*.[42] reported that osteoclastic protein (Src) does not reflect the distinct clinical behaviour of PGCG and CGCG. Martini *et al*.[32] have substantiated the role of receptor activator of nuclear factor kappa-B ligand (RANKL) as predictor of aggressive behaviour, correlating high-RANKL expression with aggressiveness and recurrence potential in CGCL. Kader *et al*.[2] hypothesised that high-p53 expression may be alarming for more aggressive clinical behaviour. Thus, a further understanding of the immunohistochemical parameters that could distinguish non-aggressive from aggressive CGCL or GCT from CGCL will have a good impact on selecting treatment options and thus affecting the outcome.

Table 4: Immunohistochemical studies associated with treatment of GCLs of jaws

Author	Group	Sample Size			IHC Marker studied	Interpretation	Conclusion
		Total	NA	A			
Tobón-Arroyave *et al*.[56]	CGCG	37	10	27	1. Glucocorticoid receptors 2. Calcitonin Receptors 3. RANK	1. Both A- and NA-CGCG significantly correlated with RANK expression and SID score. 2. Expression of RANK showed macrophages-like mononuclear cell and osteoclast-like MGCs. 3. MGCs, endothelial cells, MSCs, and spindle-shaped cells showed a strong immunoreactivity for GRα. 4. A significant difference was seen for both CTR expression and SID score between clinical forms of CGCG.	1. Phenotypic differences were observed in MGCs and osteoclasts. 2. Role of RANK, GRα, and CTR suggested a role for these receptors in the resorptive activity of CGCG may lead to a more effective use of therapeutic inhibitors of bone resorption for the treatment of CGCGs.
Vered *et al*.[57]	CGCG	41	–	–	1. Glucocorticoid receptor 2. Calcitonin receptors	Positivity for GR and/or CTR for CGCG supported the use of intralesional steroids and calcitonin as therapeutic agents in selected cases.	Altered biological behaviour in CGCG may be attributed to phenotypic transformation of constitutional cells. So, treatment might depend on its evolution.
Vered *et al*.[58]	CGCG	–	5	–	1. Calcitonin receptors 2. Glucocorticoid receptors	Calcitonin treatment was associated with changes in the expression of both CTR and GR.	Evaluation of CTR and GR should be done at different times during calcitonin treatment and based on that adjustment in treatment should be made.
Nogueira *et al*.[59]	CGCL	18	9	9	1. Glucocorticoids receptors 2. Calcitonin receptors	1. In CGCG, MSCs and MGCs express CTR and GR. 2. MGCs might be similar to osteoclasts and macrophages/histiocytes.	1. Calcitonin and intralesional steroids injections can be used to treat CGCLs. 2. Immunohistochemical staining for GR a tool to select therapeutic strategy.
Martins *et al*.[60]	CGCL	31	20	11	1. Glucocorticoid receptor 2. Calcitonin receptor 3. Osteocalcin	1. No difference between GR and CTR expression either in A- or NA-CGCLs was seen. 2. MSCs in A- and NA- CGCLs showed lesser and higher expression of osteocalcin, respectively. 3. GCs are formed by the fusion of MSCs-expressing CTR.	Both NA- and A-CGCLs could be treated with intralesional glucocorticoids and/or spray or subcutaneous injection of calcitonin.
Batista Severo *et al*.[61]	CGCL	44	22	32	1. Calcitonin receptor 2. Glucocorticoid receptor	1. GCs were formed by the fusion of CTR-positive MSCs. 2. Both NA- and A-CGCLs showed diffuse and similar positivity for both receptors. 3. MGCs were a mixture of osteoclastic and macrophagic/histiocytic cells.	Expression for CTR and GR does not influence the response to clinical treatment with triamcinolone.

A=Aggressive, CTR=Calcitonin receptor, GR=Glucocorticoid Receptor, GC=Giant cells, GCG=Giant Cell Granulomas, GCT=Giant cell tumor, GCL=Giant cell lesions, MGC=Multinucleated giant cells, MSC=Mononucleated stromal cells, NA=Non-aggressive, SID=Staining Intensity Distribution

Angiogenesis and GCLs

Angiogenesis has been implicated as a significant factor linked with the aggressiveness of GCLs.[45] Target molecules used to assess the angiogenic activity with variable results are VEGF, von Willebrand factor, CD34, CD31, and CD105.[23-24,41,51] No significant differences were observed in the angiogenic activity of PGCL and CGCL suggesting that the distinct clinical behaviour of these lesions is independent of the number of vessels and angiogenesis.[23] Microvessel density is being used as prognostic indicator for clinical behaviour of several tumors but was not found to be significantly associated with behaviour of GCLs further fueling the idea that aggressiveness of these lesions is independent of angiogenic potential.[8] Several studies have been published with very contrasting results regarding the angiogenic potential of GCLs of jaw, thus further necessitating the validation of role of angiogenesis in determining behaviour of these lesions. Antiangiogenic therapy is used as one of the mainstay treatment options for these lesions and its rationale needs to be further explored and validated.[69]

Management of GCLs

Management of GCLs varies from conservative surgery with or without adjunctive treatment for non-aggressive subtype to en-bloc resection for the aggressive subtype. Non-surgical modalities, such as subcutaneous or nasal calcitonin, intralesional corticosteroid injections, Denosumab, interferon alpha-2a, and bisphosphonates

have been proposed as an alternative option.[57,59-61,70] Vered *et al*.[58] have observed that selecting the treatment modality for CGCG is quite arbitrary; necessitating the use of a reliable and practical tool for selecting an appropriate therapeutic agent. They proposed that the relative percentage of immunohistochemically stained mononuclear and giant cells for glucocorticoid and/or calcitonin receptors can serve the purpose. Experimental evidences reveal that combination of intralesional steroids and systemic calcitonin therapy could yield a synergistically advantageous clinical outcome.[56,61] Therefore, the need of the hour is detailed evaluation of immunohistochemical markers that target cell cycle proteins, pro- and anti-apoptotic molecules, and angiogenic markers to fetch precise molecular information for these lesions.[2] In future, subsequently, immunohistochemical parameters can be accepted as reliable indicators and predictors of the clinical behaviour and prognosis.[53] There is also a dire need to conduct clinical trials to find the best therapy for each lesion. Personalised treatment approach and standardised treatment protocols should be adopted related to the variations in recurrence and aggressiveness of the lesions.

CONCLUSION

This review provides an insight into the various controversies existing around PGCL, CGCL, and GCT. Various aspects of these lesions are discussed highlighting the need of long-term prospective studies and clinical trials to validate the inferences drawn from immunohistochemical-based studies. An amalgamation of IHC with genetic studies may be the solution to our quest of exploring these lesions.

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