Histopathological and Immunohistochemical Study of Giant Cell Granuloma of the Jaw and Giant Cell Tumor of Long Bones (Comparative Study)

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ABSTRACT:

BACKGROUND:

Central giant cell granuloma (CGCG) and peripheral giant cell granuloma (PGCG) are tumor like lesions that affect jaw bones, while giant cell tumor (osteoclastoma) is a tumor that affects the long bones (e.g. tubular bones). Its affection of the jaw bones is a matter of debate. Both are very similar in their histopathological features while they vary in their clinical behavior. GCT shows a more aggressive behavior than GCG.

OBJECTIVE:

To evaluate the expression of (Proliferating cell nuclear antigen) and (P53) in peripheral and central giant cell lesion of the jaw and giant cell tumor of long bones with correlation to histopathological parameters.

METHODS:

A total of 17 (GCT), 15 (CGCG) and 16 (PGCG) cases where enrolled in this study. Immunohistochemical staining with PCNA and P53 monoclonal antibody was performed.

RESULTS:

A non-significant difference in proliferative activities was recorded among different histological giant cell lesion subtypes. Giant cell granuloma expressed the same proliferative potential to that of giant cell tumor, moreover PCNA expression was not statistically correlated to different histopathological paramters of lesion subtype.

On the other hand. The anti-apoptotic potential of giant cell granuloma which expressed by anti P53 monoclonal antibody was the same of that of giant cell tumor.

CONCLUSION:

Results of this study proved that the biological behavior namely P53 and PCNA activities was comparable between giant cell lesions and giant cell tumor. This suggest that these two conditions may act as one disease entity with a spectrum of clinical behavior, possibly due to certain differences in anatomical location which by itself affect its biological behavior. This hypothesis needs further verification concerning the clonality of the lesion to be accepted or refused.

KEY WORD: central giant cell granuloma, Peripheral giant cell granuloma, Giant cell tumor

INTRODUCTON:

Many lesions of the jaws contain giant cells, they include Peripheral giant cell granuloma, Central giant cell granuloma, aneurismal bone cyst, brown tumor of hyperparathyroidism and early stage of cherubism. Giant cell granuloma which is a benign bone lesion that occurs mainly in the jaws are not tumor but tumor like conditions, the cause of tumor like condition is chronic truma with superimposed infection. Giant cell granuloma presents either as central or peripheral giant cell granuloma (osteoclastic type). They are of unknown origin located more frequently in the mandible than maxilla, occurring in the 2nd and 3rd decades of life. Females are more frequently affected than males [7, 14].

PGCG is the most common giant cell lesion of the jaws. It arises from periosteum or periodontal membrane as a slowly growing mass that may increase in size and interfere with eating [2, 3]. On the other hand giant cell tumor is a low grade locally aggressive malignant neoplasm that develops within the long bone and apparently arises from the mesenchymal cells of the connective tissue frame work. These cells differentiate into fibroblast-like stromal components and multinucleated cells of osteoclastic type [4,5, 16].

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The histological features of each of these lesions are markedly similar although they vary substantially in their clinical behavior. However, sometimes they switch from relatively indolent growth pattern to become rapidly enlarging and destructive one with recurrence tendency. Controversy still exists whether the CGCG that occurs in the jaws is a true neoplasm and identical to those occurs in the long bones [6,7,15].
Central giant cell granuloma has two variants one granuloma and the second as tumor.
The majority of investigators now acknowledge that although most are not aggressive, lesions do occasionally occur in the jaws that are identical to the aggressive, high grade lesions that are some times found in the extremities, when this type occurs, the lesion should be referred to as CGCT. [8, 3] .
Therefore this study was conducted on GCL (CGCG, PGCG of the jaws and GCT of long bones) for the evaluation of the molecular mechanisms responsible for the biological behavior, to compare what is considered as a tumor i.e. GCT, with what is considered as a reactive granulomatous lesion (CGCG and PGCG). This was the main objective which was performed by characterizing biological markers associated with proliferation (PCNA) and apoptotic potential (p53) by means of immunohistochemistry.

MATERIAL AND METHODS:

Fourty eight giant cell lesion cases diagnosed in department of pathology in both college of dentistry (Baghdad University) and medicine during the period 2000 to December 2006.
The (H&E) stained slides for all cases were reviewed by two histopathologists. The positive control slides were prepared from 12 blocks of patients having tissue known to contain the target antigen against which the primary antibodies used in this study was reactive.
Nine of these blocks of patient having sequamous cell carcinoma, one block having breast carcinoma, while the other one was for a patient having Burkitts lymphoma.
Immunohistochemical expression recorded in percentage of stained stromal cells more than 5% as positive low expression, while moderate expression of 25%-50%, and percent more than 50% considered as high expression. Positive expression of P53 and PCNA proteins in stromal cells gives clear cut nuclear staining. Histopathological examination includes counting of mitoses, number of giant cell, number of nuclei per giant cells and necrosis.

RESULTS:

PCNA positive expression was detected in 29 of the studied group of patients (60.41%), while 19 (39.58%) patients were considered negative for PCNA either because of complete absence of any nuclear staining or the present of positive stromal cells less than 5% between them as illustrated in table (2).
P53 positive staining was detected in 4 out of 31 cases of giant cell lesion (12.90%), three cases that showed a low expression were central giant cell granuloma. and the remaining
one case that showed high expression was peripheral giant cell granuloma. While 4 out of 17 cases of giant cell tumor (23.52%) were positive for p53 proteins (2 cases showed low expression and other 2 cases showed high expression).No significant difference was shown between them as shown in table (3).
Evaluating the results of P53 and PCNA expression for all giant cell lesion subtypes in relation to various histopathological parameters showed no correlation between them with the exception of one moderate direct correlation between p53 expression and the mitotic index of giant cell tumor of long bones (R-value=0.532) as demonstrated in table (1). Moreover a non-significant difference was found between giant cell lesion subtypes in relation to various histopathological parameters (number of giant cell, nuclei per giant cell and mitotic index) as shown in table (4).

DISCUSSION:

Many researchers considered that GCG (CGCG and PGCG) and GCT share a number of similarities and dissimilarities with respect to their histological features. They found that there was no significant histological difference between them with the exception of necrosis which was higher in giant cell tumor. The results of this study confirmed this finding with others [12,13] where by necrosis which was demonstrated in 6 cases 12.5% of giant cell tumor, while it was in 4.16% (2 cases) of GCG
Thus, it appears that understanding the molecular mechanism of CGCG is important for the explanation of its clinical behavior. Accordingly based on the clinical and radiographical features, a group of investigators have divided the CGCG into two categories Aggressive lesions which are characterized by pain, rapid growth, cortical perforation, root resorption and marked tendency to recur, and a non-aggressive lesions which exhibit few or no symptoms are of slow growth and do not show cortical perforation or root resorption of teeth involved in the lesion [7].
Similar to the present study, Pogrel with Kaban and Dodson in 2003 [4, 5] presented a comparison on CGCG of the jaws with GCT of long bones and giant cell reparative granuloma of small bones indicated that these lesions are histologically and a pathogenetically similar.

The histopathogenesis of these lesions appear to be nearly identical and the biological behavior of CGCG of the jaws is more closely aligned with GCG of small bones than with the more aggressive GCT of long bones [12, 13 ,18].

It's worthy here to mention that according to the similarity of the biological behavior of CGCG of the jaw with that of GCT of long bones, CGCG of the jaw may be considered

as a low grade tumor and the differences between both may be due to the variations in the anatomical sites, since the presence of the teeth in addition to the histological structure of the jaw bone and bone marrow activity, could influence the biological behavior of CGCG comparatively.

Noteworthy, that one of the cases that has been diagnosed initially as CGCG kept recurring despite treatment and produced nodal metastasis after 4 years of presentation yielded very high p53 expression and positive PCNA expression. Therefore these findings suggested that, high p53 expression may alert us to a more aggressive clinical behavior.

Finally, it should be pointed that the recurrence rate of CGCG and GCT was 40%-45.5% [17] and that of PGCG was 10% or more [1,19]. Similar recurrence rates (11%-49%) were reported for CGCG by [20,21]and that of GCT was 40%-60% [22]. This support the hypothesis that what is considered giant cell granuloma is actually a tumor process with a spectrum of biological behavior.

CONCLUSION:

1- A non-significant correlation was observed in this study between the proliferative activity using (PCNA and P53 as antiapoptotic) of different lesion subtypes with various histopathological parameters (number of giant cells, number of nuclei per giant cells and mitotic index).with the exception of one moderate direct correlation between p53 expression and the mitotic index of G.C.T. of long bones.

Suggestions:

1.Long-term follow up studies of the recurrent giant cell lesions of the jaws cases to elucidate the prognostic value of PCNA and p53 as proliferative and apoptotic markers in these lesions including large number of cases.

2.Giant cell lesions of the jaw require careful surgical treatment and contenuous follow-up to determine its prognosis.

3.Further detailed studies on different immunohisochemical markers that

deal with cell cycle, pro and anti-apoptotic, angiogenic and other invasive properties, must be performed to provide precise molecular information for these lesions.

4.Molecular studies on osteoprotegrin proteins (inhibition of resorption) with ligands (initiation of resorption) and its receptor protein (RANK) which is responsible for the osteoclastogenesis of G.C.L. are highly recommended for these clinical entities to highlights some information about their biological behavior.

Table 1: Correlation coefficient between p53 and PCNA expression with different histopathological parameters for all lesion subtypes

Lesion types	Variables	PCNA		P53	
		R	P-value	R	P-value
C.G.C.G	No. of Giant	-0.047	0.868	0.246	0.377
	No.of nuclei	-0.343	0.210	-0.283	0.306
	Mitotic Index	0.326	0.236	0.307	0.266
P.G.C.G	No.of Giant	0.378	0.149	-0.305	0.250
	No.of nuclei	0.034	0.900	-0.218	0.417
	Mitotic Index	-0.228	0.395	-0.082	0.764
G.C.T	No. of Giant	-0.351	0.167	-0.196	0.451
	No.of nuclei	-0.111	0.672	-0.143	0.583
	Mitotic Index	0.081	0.759	0.531*	0.028

∗ : ***Significant difference.***

Table 2: Statistical differences (T-test) in PNCA expression between different histological types

Lesion type	N	Mean % ± SD	t-test	P-value	Sig.
CGCG	15	14.333±20.440	1.228	0.229	N.S
PGCG	16	7.688±6.954			
CGCG	15	14.333±20.440	0.949	0.350	N.S
GCT	17	9.059±9.810			
PGCG	16	7.688±6.954	0.461	0.648	N.S
GCT	17	9.059±9.801			
CGCG+ PGCG	31	10.903±15.184	0.451	0.654	N.S
GCT	17	9.059±9.801			

N.S: Non Significant difference

Table 3: Chi-square test between p53 expression and giant cell lesion subtypes

Giant cell lesion type	P53 expression		Chi-Square test	P-value	Sig.
	+ve	- ve			
Granuloma	4	27	0.893	0.345	N.S
Tumor	4	13			

N.S: Non Significant difference.

Table 4: T- test difference between any two of lesion types and histopathological parameters (no. of giant cells, no. of nuclei and mitotic index

	Lesion type	N	Mean % ± SD	T-test	p- value	Sig.
Lesion types and mitotic index	CGCG	15	3.787 ± 1.987	0.94	0.35	N.S
	PGCG	16	3.112 ± 1.250			
	CGCG	15	3.787 ± 1.987	1.02	0.32	N.S
	GCT	17	2.862 ± 3.066			
	PGCG	16	3.112 ± 1.999	0.28	0.78	N.S
	GCT	17	2.862 ± 3.066			
	CGCG+PGCG	31	3.440 ± 1.990	0.70	0.49	N.S
	GCT	17	2.862 ± 3.066			
Lesion types and no. of nuclei per giant cells	CGCG	15	9.933 ± 1.870	1.328	0.194	N.S
	PGCG	16	10.688 ± 1.250			
	CGCG	15	9.933 ± 1.870	1.298	0.204	N.S
	GCT	17	13.765 ± 11.278			
	PGCG	16	10.688 ± 1.250	1.084	0.287	N.S
	GCT	17	13.765 ± 11.278			
	CGCG+PGCG	31	10.323 ± 1.600	1.683	0.099	N.S
	GCT	17	13.765 ± 11.278			
Lesion types and no. of giant cells	CGCG	15	5.800 ± 12.65	0.255	0.801	N.S
	PGCG	16	5.938 ± 1.692			
	CGCG	15	5.800 ± 1.265	0.559	0.581	N.S
	GCT	17	6.159 ± 1.345			
	PGCG	16	5.938 ± 1.692	0.229	0.821	N.S
	GCT	17	6.059 ± 1.345			
	CGCG+PGCG	31	5.871 ± 1.477	0.434	0.666	N.S
	GCT	17	6.059 ± 1.345			

N.S: Non Significant difference.

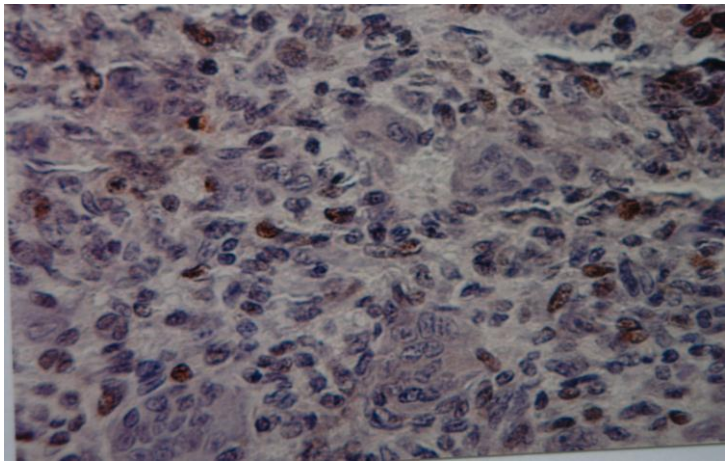

Figure 1: Positive IHC staining of anti(PCNA) antibody in stromal cells of CGCG showing nuclear staining.

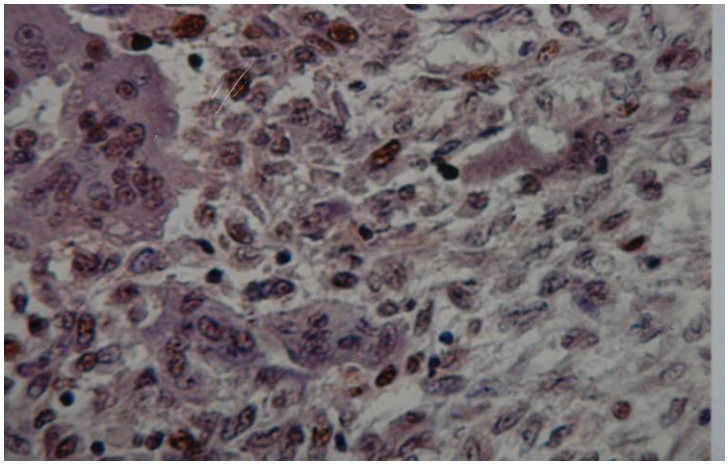

Figure 2: Positive IHC staining of anti (PCNA) antibody in stromal cells in GCT (40X) showing nuclear staining.

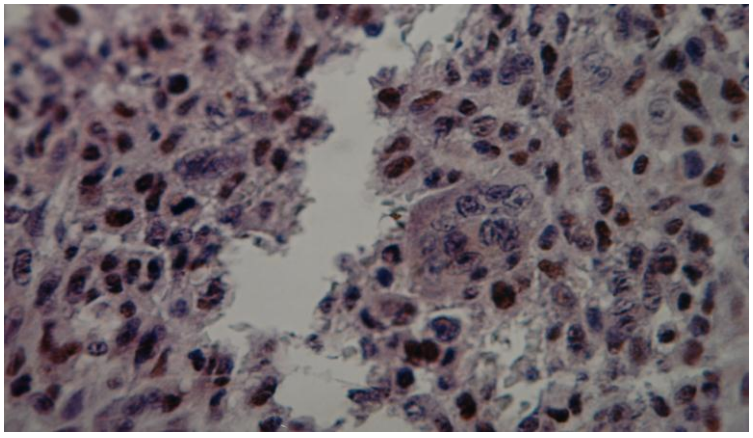

Figure 3: Positive IHC staining of anti (PCNA) antibody in stromal cells in PGCG (40X) showing nuclear staining.

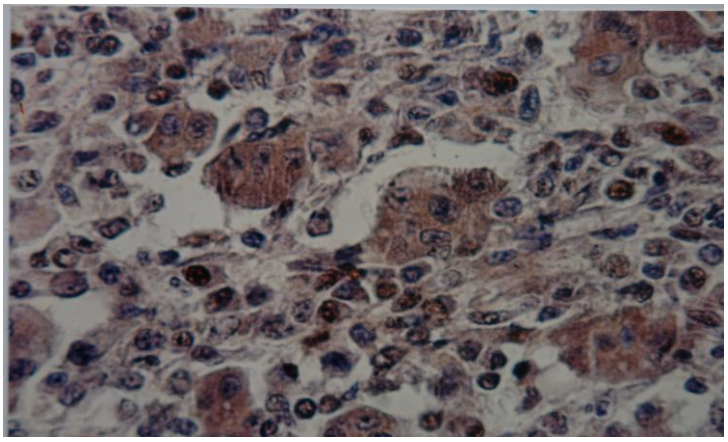

Figure 4 :IHC staining wiht anti(P53)antibody in stromal cells in CGCG of the jaws(40x) showing nuclear staining.

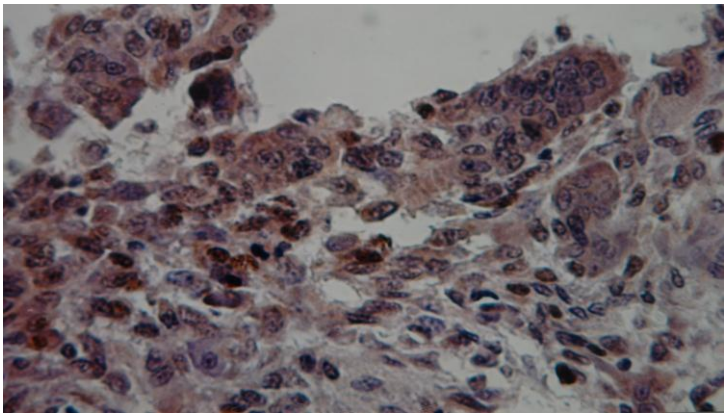

Figure 5: Positive IHC staining with anti (P53) antibody in stromal cells in PGCG of the jaws (X40) showing nuclear staining.

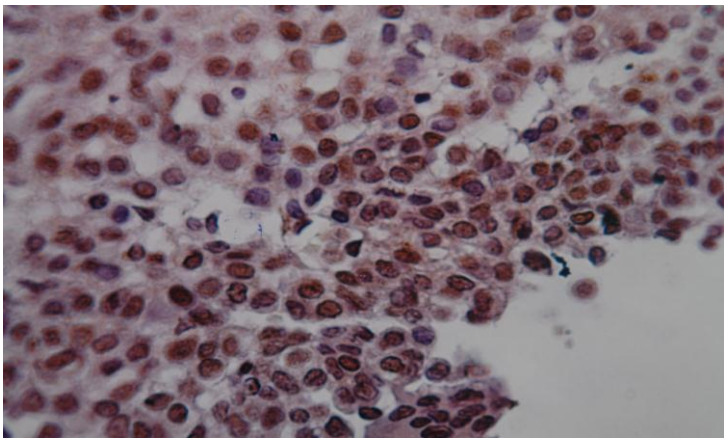

Figure 6: Positive IHC staining with anti (P53) antibody in stromal cells in GCT of the maxillary jaw (X40) showing nuclear staining.

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