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Evaluation of the Expression of Cylin D1 and CD10 in Giant Cell Bone Tumor: An Immunohistochemical Study

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Abstract

Background: The predictive role of radiological and histological classification of giant cell bone tumors has been disputed. Moreover, some malignant tumors including sarcoma and carcinoma harbor similarity with giant cell bone tumors. Application of molecular biomarkers can help to avoid these mimics and share for better understanding of its biological behavior. The current study investigates the immunohistochemical expression of cyclinD1 and CD10 in giant cell bone tumors and analyzes their relation with clinicopathological findings.

Aim of Study: Evalute immune histochemical expression of Cyclin D1 & CD10 in giant cell tumors and analyze their relation with clinico-pathological finding.

Material and Method: Immuno-histochemical expression of cyclin D1 and CD10 in 25 specimens of giant cell bone tumors were studied. The relationship between their expression and the clinico-pathological variables were also investigated.

Results: Nuclear cyclin D 1 immuno-staining was observed in 40% of multi nuclear giant cells and complete absence in stromal cells in the same time the study found a statistical correlation between its expression and both of recurrence (p=0.001) and aggressiveness (p=0.012) of studied cases. Membranous CD10 immuno-expression was exclusively observed in 80% of stromal mononuclear cells with significant correlation with aggressiveness (p=0.23) and recurrence (p=0.014).

Conclusion: Although radiological and histological classification provides essential findings for giant cell bone tumor diagnosis, molecular markers (cyclin D1 and CD10) could be considered as independent predicting factors for GCT. Cyclin D1 can be considered as a prognostic marker to predict its behavior. CD10 is exclusively expressed in the neoplastic mononuclear cells, raising its possible role in the giant cell bone tumor pathogenesis.

Key Words: *Cyclin D1 – CD10 – GCT.*

Introduction

GIANT cell tumor of bone (GCT) is known as benign locally aggressive tumor that accounts for about 5 % of primary bone tumors with high recurrent incidence and rare metastasis [1]. Its peak incidence is between the third and the fourth decades with slight female predominance [2]. These neoplasms are histologically consisted of stromal mononuclear cells (MC), macrophages and uniformly distributed multinuclear giant cells (MNGC) [3]. The diagnosis of GCT practically depends on radiological and histological features correlation. However, radiological and microscopic findings in some patients have similarity with another serious lesions including giant cell osteosarcoma and carcinoma [4]. Furthermore, the prognostic value of Jaffe histological grading system [5] and radiological classification of Campanacci had become limited [6]. In such situation, immunohistochemistry application is highly required for more accurate final diagnosis and proper interpretation; especially with small core biopsies [7]. The cell division is controlled by an ordered series of cell cycles that in turn, are regulated by more than identified 15 cyclins and cyclin-dependent kinases (CDKs) [8]. The aggressiveness of tumors is often associated with elevated cell cycle replication, besides the recurrence potential of GCT was controversially linked to cyclin D1 [9]. A common acute lymphoblastic leukemia antigen (CALLA), known as CD 10, is a zinc-dependent metallopeptidase which is essential for cleavage of neuropeptids and peptide hormones. It has an significant role in the classification of B-lineage lymphomas. It is also expressed on several neoplastic hematopoietic, lymphoid and epithelial cells as, renal cell carcinoma, solid-pseudo papillary tumor of the pancreas and follicular lymphoma [10]. The current study is aimed to analyze the immuno histochemical expression of cyclin D 1 and CD 10 in GCT, as well as evaluate their correlation with the recurrence rate and aggressiveness.

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Material and Methods

Archived records and tissue (paraffin blocks) from 25 patients with histopathologic diagnosis of GCT in Pathology Department, Benha faculty of medicine, were collected from 2015 to 2021for this retrospective study. All cases were fixed in 10% formalin after surgical procedures (resection or curettage). Demographic data of studied cases were obtained from archived files. The cases were graded radiologically according to Campanacci imaging classification into: Grade I (no=9); with well-defined margin and an intact cortex, grade II (no=6): Active lesions with a relatively well-defined margin and moderately expanded thin cortex, grade III (no=10): Aggressive lesions with indistinct borders and cortical destruction Fig. (1A,B). All cases with brown tumor, inadequate tissue for sectioning or unavailable clinical and/or radiological data were excluded. Approval from Ethical Committee in Benha Faculty of Medicine (Rc2.10.2020) was taken for the study protocol.

Hematoxylin and eosin sections were examined to confirm diagnosis and histologically graded according to Jaffe histological grading system into: Grade I (no=7); with numerous MNGC, grade II (no=8): Numerous mononuclear cell with moderate atypia, and grade III (no=10) with mitosis and few, small MNGC. Estimation of the recurrence in GCT requires follow-up minimum ≥2 years and the mean time for detection of recurrence was 15.5 ± 11.1 months **[11]** and the aggressiveness was determined according to fore-mentioned Campanacci classification, in which radiological grade III was considered as aggressive group of giant cell tumor.

Kaplan Meier curve was used to determine survival probability among the patients according to the levels of the studied markers. Log-Rank test was used to compare survival between groups. The accepted level of significance. In this work was stated at 0.05 (p<0.05) was considered significant. Recurrence was defined as a recurrent GCT thatwas histologically confirmed after the initial curettage and/or surgical excision.

Immunohistochemistry:

Sections were prepared at 4 µm thickness from each tissue block. The sections were deparaffinized in an oven at 60°C for 30min and then put in xylol for 10min, rehydrated in graded ethanol. Endogenous peroxidase activity was blocked by using 0.5% hydrogen peroxide for 5 minutes, followed by washing in phosphate-buffered saline solution (PBS) for 5 minutes. Slides were immersed in deionized water and then rinsed in PBS, followed by sodium citrate solution as antigen retrieval (pH 6). Sections were incubated with primary antibody cyclinD 1 (Monoclonal rabbit anti-cyclin D1, Clone: SP4, Catalog Number: RM-9104-S1, Lab vision, Fremont, California, US) at dilution 1:50 for 60 minutes/room temperature and CD 10 (Monoclonal rabbit anti-CD10, Clone: 56C6, Vantana, Tucson, US) ready to use for 30 minutes. Slides were counterstained with hematoxylin, washed with water, dehydrated after treated with the DAB solution, mounted on slides, and observed under a microscope. Breast carcinoma and tonsil were taken positive control for cyclin D1 and CD 10, respectively.

Interpretation:

The immuno-staining was examined and calculated by light microscopy, and photomicrographs were obtained using a digital camera (Olympus C-7070).

Cylin D1:

The proportion of nuclear positive staining was recorded as: 1+ :0-5% of the cells were positive; score 2+ :6-50% of the cells were positive; 3+>50% of the positive. Score Positive expression was considered if more than 5% of cells showed positive staining **[12]**.

CD 10 positivity was considered with membranous staining of >1 0% of the cells. Each case was examined andmean percentage of positive cells were calculated as follow: <10% as negative, 10-50% as low expression and >50% as high expression **[13]**.

Statistical study: The data collected were analyzed using the SPSS (statistical program for social science) software version 16.0 (SPSS Inc., Chicago, Illinois, USA). Chi-square test and/or Fisher's-exact tests were applied to evaluate the relation between variables. If p-value was found to be less than 0.05, the results were considered statistically significant and less than 0.001 the results were considered highly statistically significant.

Results

Demographics and clinical features: Ages of the studied 25 GBT, ranged from 21 to 55 years with mean age (36.84± 10.93). There were 16 (64%) female and 9 (36%) male, most of studied cases (68%) were located in distal end of femur while only (8%) were diagnosed in proximal humerous.

Immunohistochemical results:

Multinuclear giant cells of studied cases showed positive nuclear cyclin D1 expression in 10 cases (40%), 8 cases out these 10 cases were score +3 nuclear cyclin D1. In the contrast, mononuclear cells of all studied cases showed negative cyclin D1 expression (score +1) with statistically significant difference of cyclin D1 expression between multinuclear giant cells and mononuclear cells (p=0.034), as shown in Table (1), Fig. (2A,B).

Positive membranous expression of CD10 was exclusively found in all mononuclear stromal cells of all studied GCT with 44 % showed high CD 10 immuno-staining, while all multi nuclear giant cells in 100% of cases were CD10 negative, registering highly significant difference (p=0.0001) as shown in Table (1), Fig. (3A,B).

Associations of Cyclin D1 &CD10 expression to clinico -pathological parameters and patients' outcome:

Out of 10 aggressive cases 7 cases (70%) scored +3 for cyclin D1 expression and high CD 10 expression with statistically significant positive correlation was found between both of cyclin D 1 and CD 10 expression with tumor aggressiveness (p =0.012, p=0.023, respectively) Similarly, score +3 cyclin D1 expression was found in all 6 recurrent cases (100%) (p=0.0001) and 5 cases (83.3%) showed high CD10 expression (p=0.014). No significant correlation of cyclin D1expression was observed in patients with age, sex, and grade, as shown in Table (2).

Kaplan-Meier analysis:

In the Kaplan-Meier plot, a significant difference in RFS was present among cases with positive and negative cyclin D 1 staining (log rank test =14.754, p=0.000), but CD10 expression was insignificantly correlated with RFS (log rank test =0.018, p=0.895). The Kaplan-Meier plots for Cyclin D 1 and CD 10 are illustrated in in Fig. (4).

Table (1): Expression of Cyclin D1 and CD10 in studied cases.

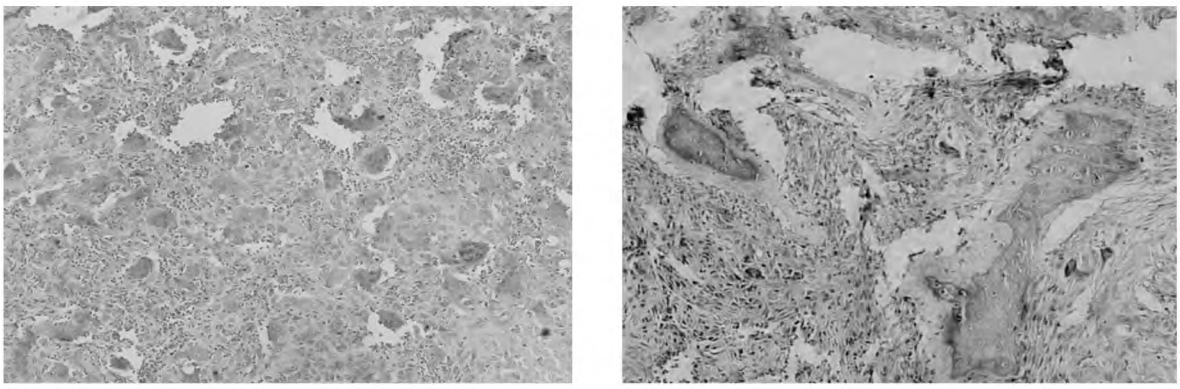
	Giant cells No (%)	Mononuclear cells No (%)	p-value
Cyclin D1:			
+1 (negative)	15 (60%)	25 (100%)	0.034*
+2	2 (8%)	0%	
+3	8 (32%)	0%	
Total	25	25	
CD10:			
Negative	25 (100%)	5 (20%)	0.0001**
Low expression	0%	9 (36%)	
High expression	0%	11 (44%)	
Total	25	25	

* Statistically significant.
**Highly statistically significant.

Table (2): Relation between CD10 & Cyclin D1 expressions and both clinico-pathological findings.

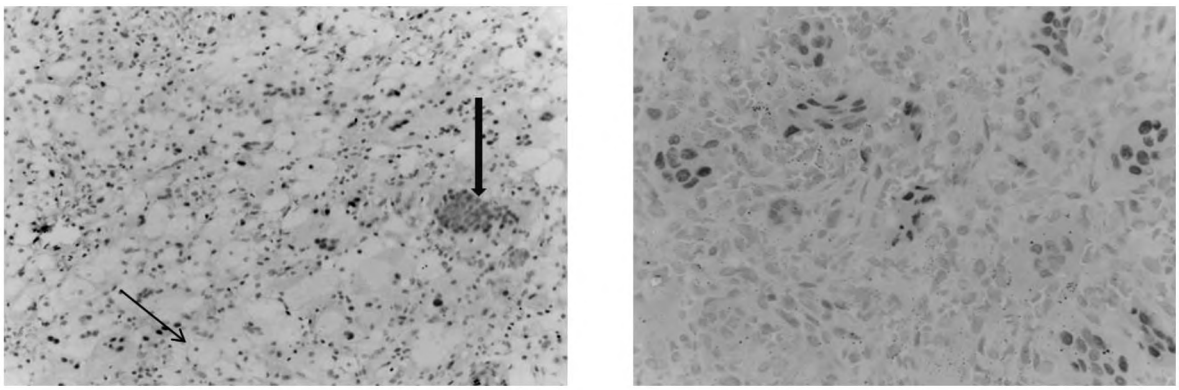
Clinical data	Cyclin D 1				CD10			
	+1 (–ve) No (%)	+2 No (%)	+3 No (%)	p-value	Negative No (%)	Low expression No (%)	High expression No (%)	p-value
Age:								
≤30 (n=11)	3 (27.3%)	2 (18.2%)	6 (54.5%)	0.3	2 (18.2%)	0 (0%)	9 (81.8%)	.103
>30 (n=14)	12 (85.7%)	0 (0%)	2 (14.3%)		3 (21.4%)	9 (64.3%)	2 (14.3%)	
Sex:								
Male (9)	5 (55.6%)	0 (0%)	4 (44.4%)	.510	2 (22.2%)	5 (55.6%)	2 (22.2%)	.256
Female (16)	10 (62.5%)	2 (12.5%)	4 (25%)		3 (18.8%)	4 (25%)	9 (56.2%)	
Grading:								
Grade I (n=7)	5 (71.4%)	0 (0%)	2 (28.6%)	.276	3 (43%)	2 (28.5%)	2 (28.5%)	.141
Grade II (n=8)	7 (87.5%)	1 (12.5%)	0 (0%)		0 (0%)	7 (87.5%)	1 (12.5%)	
Grade III (n=10)	3 (30%)	1 (10%)	6 (60%)		2 (20%)	0 (0%)	8 (80%)	
Tumor site:								
Femur (n=17)	8 (32%)	1 (4%)	8 (32%)	0.1	5 (20%)	3 (12%)	9 (36%)	.888
Tibia (n=6)	5 (20%)	1 (4%)	0 (0%)		0 (22.5%)	4 (66.7%)	2 (33.3%)	
Humerus (n=2)	2 (100%)	0 (0%)	0 (0%)		0 (0%)	2 (100%)	0 (0%)	
Aggressiveness:								
Non-Aggressive (n=15)	12 (80%)	2 (13.3%)	1 (6.7%)	0.012*	4 (26.7%)	7 (46.6%)	4 (26.7%)	0.023*
Aggressive (n=10)	3 (30%)	0 (0%)	7 (70%)		1 (10%)	2 (20%)	7 (70%)	
Recurrence:								
Non-recurrent (n=19)	15 (79%)	2 (10.5%)	2 (10.5%)	0.0001**	4 (21.1%)	9 (47.4%)	6 (31.5%)	0.014*
Recurrent (n=6)	0 (0%)	0 (0%)	6 (100%)		1 (16.7%)	0 (0%)	5 (83.3%)	

*Statistically significant. **Highly statistically significant.



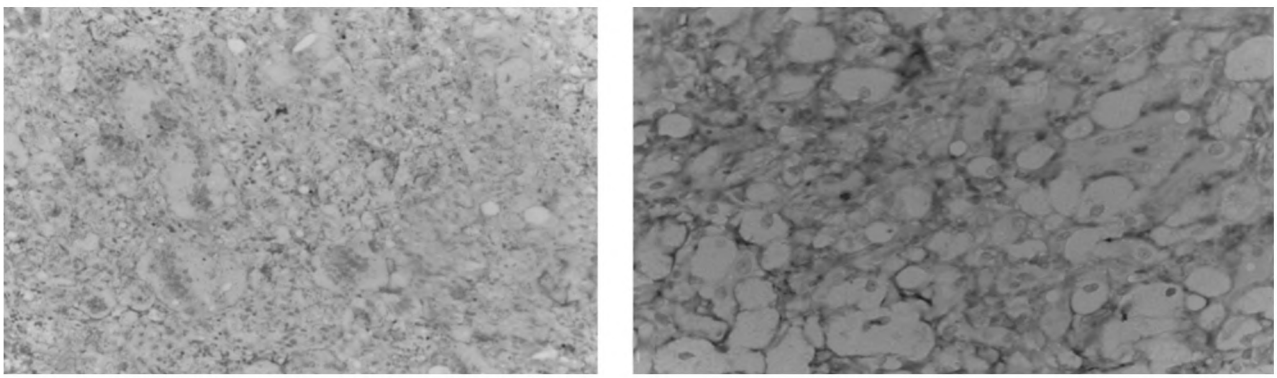
(A) (B)

Fig. (1): (A) GCT (grade I) showing multiple evenly spaced MNGC with stromal mononuclear cells (H&E x200). (B) GCT (grade III) showing few MGFC with many spindle shaped, pleomorphic stromal cells invading osteoid tissue (H&E x200).



(A) (B)

Fig. (2): (A) Positive nuclear cyclin D1 expression in MNGC (blue arrow) compared with negative expression in mononuclear cell (red line) (IHC x200). (B) Score +3 nuclear cyclin D1 expression in MNGC (IHC x400).



(A) (B)

Fig. (3): (A) Positive membranous expression of CD10 stromal cells compared to negative expression in MNGC (IHC x200). (B) High membranous positive CD 10 expression in stromal cells (IHC x400).

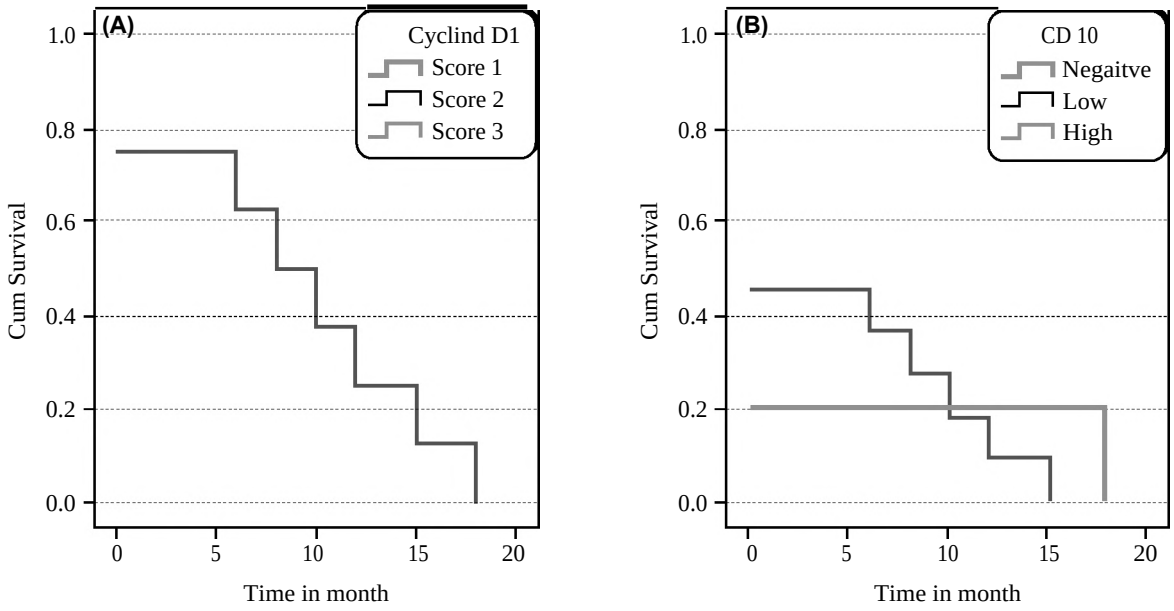


Fig. (4): Kaplan-Meier curve for recurrence free survival according to cyclin D1 expression (A) and CD10 expression (B).

Discussion

The clinical outcome of giant cell bone tumor (GCT) is difficult to predict based only on its microscopic and radiological findings. Although many classification of GCT have been established, little prognostic information about its clinical course is provided **[14]**. Additionally, its biological properties are still inaccurately predicated and precisely needed to be better understood. The current study aimed to put more light on its biological behavior. The immunohistochemical expression of cyclin D1, one of cell cycle regulatory proteins, was analyzed in mononuclear stromal cell and multinuclear giant cells. This work demonstrated significantly cyclin D1 overexpression in multinuclear giant cells more than mononuclear cells (p=0.034). In addition, cyclin D1 immunostaining of multinuclear giant cells in recurrent and aggressive groups was significantly higher than non-recurrent and non-aggressive ones (p=0.0001 and 0.012, respectively). This is in line with results of other studies **[15,16]**. Cyclin D1 was expressed in multinuclear giant cells and complete absence in mononuclear cells of GCT in the study done by Eréndira et al., (2017) **[17]**, that matched our results. Similarly, Kauzman et al., (2003) **[18]** found that 72% of multinuclear giant cells showed >50% cyclin D1 positivity while 85% of mononuclear cells showed <5% of cyclin D1 expression. Cyclin D 1 immunostaining of both recurrent and aggressive GCT was statistically different from its expression in non-aggressive and non-recurrent ones (p=0.038) in published reports **[19]**, that is in keeping with our results. Mate et al., (2019) **[20]** was in agreement with our results concerning overexpression of cyclin D1 in multinuclear giant cells , as well as demonstrating a significant correlation with recurrence potential and aggressive behavior, but with no significant difference between aggressive and non-aggressive GCT, in the contrast of our findings. This may be due to that not all grades of GCT were involved in his study. Within central giant cell granuloma of the jaw, no statistical correlation between cyclin D1 and aggressiveness of the lesion **[21]**. The current work was consistent with association between an accelerated cell cycle progression and less favorable outcome of the tumors in line with several results e.g. in renal cell carcinomas and breast **[22,23]**. Stromal cyclin D1 induces the secretion of macrophage-colony stimulating factor (M-CSF) and osteopontin (OPN) as established in published reports **[24]**. Monocytes are engaged to form multinuclear giant cells through paracrine signaling with the help of macrophage-colony stimulating factor (M-CSF). Moreover, Osteopontin, in turn accelerates the osteolytic activity of osteoclast giant cells **[25]**. This may explain why the aggressive behavior of GCT is related to increased cyclin D1 expression. On evaluation of other cell cycle markers, both multinuclear giant cells and mononuclear cells were p53 negative expression and MDM2 was positive only in mononuclear cells **[26]**. After reviewing the literature about expression of cell cycle markers in GCT, It has shown its unpredicted and controversial role of cyclin D1 in the pathogenesis of multinuclear giant cells that has been elucidated by the following points: (1) Interestingly, cyclin D 1 was absent in giant cells of other granulomatous

lesions, like Langhans-type giant cells (LHGCs), supporting its unique role in pathogenesis of giant cells in GCT **[27]**. (2) The current work revealed cyclin D1 over expression in the multinuclear giant cells. Moreover, the negative expression of cyclin B1 (responsible for G2-M phase transition) and Ki-67 in multinuclear giant cells were statedin other researchers that may reflect a limited mitotic division (proliferative activity) and high metabolic state of multi nuclear cells **[28]**. On the light of that, cyclin D1 has crucial role in tumor genesis of GCT **[29]**. Beside the role of Cyclin D1, suggested by the current work, in the pathogenesis and formation of multinuclear giant cells, its overexpression in all cases and correlation with recurrence adding prognostic significance to predict the clinical course of GCT.

CD 10, cell surface glycoprotein, was primitively known as a cell marker to identify and differentiate between hematological malignancies as It is expressed specifically in early lymphoid progenitor stages **[30]**. However, CD10 is expressed in non-hematopoietic normal tissue like skin and non-hematopoietic tumors including genitourinary and gastrointestinal tract tumors with apical and luminal expression pattern suggesting its vital role in secretory process of these tumors **[31]**. Within the current study, mononuclear stromal cells of all studied cases exclusively showed positive CD 10 expression with membranous distribution while multinuclear giant cells of all studied cases showed negative CD 10 expression. The current study found a prognostic value of CD 10 as its expression was significantly higher with the recurrence and aggressive behavior of GCT studied cases (p=0.014 and 0.023, respectively). After reviewing the literature, expression of CD10 in GCT was evaluated in only one study done by Al-Abbadi et al., (2016) **[31]** whose results support our findings regarding unique CD10 expression in mononuclear cells. However, the same study didn't analyze the predictive value of CD 10 in GCT to interpret with the current work. CD 10 was expressed in esteoblast and cultured osteoblast-like cells that strengthens the neoplastic origin of osteoblasts cells in GBT, that can explain its exclusive expression in stromal mononuclear cells **[31]**. Since GCT showed positive CD 10 reaction, positive CD 10 lytic bone lesions including renal cell carcinoma should be differentially diagnosed from GCT especially with core biopsies or very small submitted samples. Stromal cells of Amelobtastoma (locally invasive tumor) showed mainly membranous CD 10 staining with significant correlation to aggressive clinical behavior that is somewhat similar to the results of the current studied GCT **[32]**.

Conclusion:

Although histological classification provides different histological findings of giant cell bone tumor, molecular markers (cyclin D 1 and CD 10) could be considered as independent predicting factors for giant cell bone tumor. Cyclin D1 has a role in the pathogenesis of giant cell formation, in the same time can be considered as a prognostic marker to predict its behavior. CD 10 is exclusively expressed in the neoplastic mononuclear cells, raising its possible role in the giant cell bone tumor pathogenesis. Additional studies are required to confirm the role of CD 10 in giant cell bone tumor.

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تقييم تعبير الدلالتين Cyclin D1 و CD10 فى أورام الخلايا العملاقة فى العظام : دراسة كيميائية مناعية

المقدمة: تتشابه بعض الأورام الخبيثة فى الصورة الإشعاعية والنسيجية مع أورام الخلايا العملاقة للعظام وتطبيق بعض الدلالات قد يساعد فى تجنب هذه المحاكاة.

الهدف: فحص دور (سيكلين د١) و (سى دى ١٠) فى أورام الخلايا العملاقة للعظام وعلاقتها بالنتائج السريرية المرضية.

طرق البحث: تمت الدراسة على شرائح موجبة من بلوكات شمعية لعينات نسيجية (٢٥) أورام الخلايا العملاقة للعظام وتم تجميعها من قسم الباثولوجى بكلية طب بنها ما بين الفترة من ٢٠١٥-٢٠٢١ وتم معالجتها بكيمياء المناعة النسيجية للكشف عن ظهور دلالة (سيكلين د١) و(سى دى ١٠).

نتائج البحث: قد وجد أنه ٤٠٪ من الخلايا متعددة النواة الأورام الخلايا العملاقة للعظام إيجابية لـ (سيكلين د١) بينما سجلت ٨٠٪ من الخلايا أحادية النواة ظهور دلالة (سى دى ١٠) وكذلك أظهرت الدراسة علاقة إحصائية طردية مع درجة عدوانية وتكرار ظهور الورم مع كلا مع الدلالتين.

ملخص البحث: يمكن اعتبار (سيكلين د١) و (سى دى ١٠) من عوامل التنبؤ لأورام الخلايا العملاقة للعظام والدور المحتمل للسى دى ١٠ فى حدوث نفس الورم.