Immunohistochemical assessment of tumor suppressor gene Wwox in relation to proliferative marker KI67 proteins expression in giant cell lesions of the jaws and giant cell tumor of long bones

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ABSTRACT

Background: Peripheral giant cell lesion (PGCL) and central giant cell lesion (CGCL) of the jaws have a distinct clinical behavior.Giant cell tumour (GCT) is a benign locally aggressive neoplasm affects the long bones. Both lesions are characterized histologically by multinucleated giant cells in a background of ovoid to spindle-shaped mesenchymal cells. The WW domain-containing oxidoreductase (*WWOX*) gene is located at 16q23.1–16q23.2, a region that spans the second most common human fragile site, *FRA16D*, at 16q23.2.The Ki-67 antigen is a nuclear protein that is associated with and may be necessary for cellular proliferation.Ki-67 protein is present during all active phases of the cell cycle (G_1, S, G_2, and mitosis), but is absent from resting cells (G_0). This study aimed to evaluate and compare immunohistochemical expression of tumor suppressor gene (WWOX) and proliferative marker (ki67) in giant cell lesions (GCLs) of the jaws and long bones.

Materials and methods: Forty five retrospective paraffin embedded tissue blocks of giant cell lesions of the jaw and long bones were included in this study.Sections were stained immunohistochemically with anti WWOX and anti ki67 monoclonal antibodies.

Results: Positive WWOX expression was found in 12 cases (80%), 14cases (93.3%)and12 (80%) of CGCG, PGCG and GCT studied cases respectively, with thehighest strong positive expression observed in PGCG.Positive Ki67 expression was found in 12 cases (80%), 13cases (86.7 %)and10(66.7%) of CGCG,PGCG and GCT studied cases respectively with the high proliferative expression score has been recorded in PGCG .Statistically highly significant difference was found in the Ki67expression among different giant lesion types (p=0.006), whilenon-significant difference was found in WWOX expression. Non-significant correlation was found between expression of WWOXand Ki67 in CGCG, PGCG and GCT studied cases.

Conclusions: Similar immunohistochemical expression of WWOX and Ki67 ingiant cell lesions of the jaw and GCT of long boneswith non-significant correlation between them in different studied lesionssuggests that those lesions may be the same disease but with different clinical behavior.

Keywords: Wwox, KI67. (J Bagh Coll Dentistry 2015; 27(1):121-127).

INTRODUCTION

Central giant cell lesion (CGCL) and peripheral giant cell lesion (PGCL) are pathological conditions of the jaws that share the same microscopic features, but differ clinically in terms of their behavior [1]. 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 [2,3]. Peripheral giant cell lesion (PGCL) is considered as a reactive process associated with a local irritating factor that shows low recurrence after treatment, especially if the irritating factor is eliminated. On the other hand, central giant cell lesion (CGCL) presents a variable clinical behavior ranging from slow and asymptomatic growth without recurrence to rapid, painful and recurrent growth [4]. The GCT of long bones is a rare benign neoplasm, characterized by local aggressiveness, high recurrence rates and metastasis to the lung [5].It 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 [6-9]. The principal characteristic of this tumor is the unpredictable biological behavior [8].

The WWOX gene (WW-domain containing oxidoreductase) is a candidate tumor suppressor gene located at 16q23.3-24.1, spanning the second most common fragile site, FRA16D [10]. The WWOX protein contains two N-terminal WW domains and a central short chain oxidoreductase-like domain [11], that mediate protein–protein interactions. WW domains mediate complexes associated with signaling pathways implicated in a variety of cellular processes such as transcriptional regulation and protein stability [12]. WWOX physically interacts via its first WW domain with the p53 homolog, p73 and induces cell apoptosis [13]. Numerous studies have correlated loss of WWOX expression with cancer development, including some associating WWOX alteration with poor prognosis and outcome in various cancer types [11], suggesting a growth advantage for tumors with loss of WWOX. Ki-67 represents a nuclear protein forming part of DNA replicase complex that provides a simple, rapid

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and reliable means of evaluating the growth fraction of neoplastic cell populations [14]. Ki-67 has a short half-life; hence it can be used as a marker for actively proliferating cells. Since it is not expressed during the resting phase of a cell cycle, it functions as a specific indicator of cellular proliferation [15].

MATERIALS AND METHODS

Forty five formalin-fixed, paraffin-embedded tissue blocks (15 cases of CGCG, 15 cases of PGCG and 15 cases of GCT) were obtained randomly from the archives of the department of Oral & Maxillofacial Pathology/ College of Dentistry/ University of Baghdad and Al-Shaheed Ghazi Hospital/ Medical City / Baghdad during the period (1976-2012). The clinical data were obtained from surgical reports available with the tissue specimens .The diagnosis of each case was confirmed by examining the hematoxylin and eosin (H&E) sections by two experienced pathologists.

Four μm thick sections were cut for immunoshitochemcial staining with anti WWOX and anti Ki67 monoclonal antibodies (Mabs) (AbcamUK). Abcam expose mouse and rabbit HRP/DAB immunohistochemical detection kit (Catalog No. ab80436, Cambridge, UK) was used for both primary antibodies (WWOX, Ki67).Negative and positive controls were included in each IHC run. Human colon carcinoma tissue blocks were used for WWOX and tonsil tissue blocks for Ki657 (according to antibodies manufacturer).

For immunohistochemistry, the sections were mounted on positively charged slides. Slides were baked in hot air oven at 65°C overnight. Sections were sequentially dewaxed through a series of xylene, graded alcohol and water immersion steps. Antigen (Ag) retrieving was done for both WWOX and Ki67 Abs as recommended by the manufacturer. Then endogenous peroxidase activity was blocked followed by blocking the non- specific staining. Primary Abs (100 ml) was applied for each section. A dilution of (1:75) for WWOX, and (1:100) for Ki67 were used. After an overnight incubation and washing with phosphate buffered solution (PBS), secondary Abs were applied, incubated and rinsed with a stream of PBS. Primary Abs were visualized with 3, 3-diaminobenzidine (DAB) chromogen, then counterstained with Mayer's hematoxyline, dehydrated and mounted.

Immunohistochemical expression recorded in percentage of stained stromal cells and multinucleated giant cells in the studied lesions was classified and scored as follows: - For WWOX, cytoplasmic or cytoplasmic/nuclearstaining pattern was considered positive for WWOX immunostaining. Immunoreactivity was classified as follows: (1) negative <10%, (2) weak positive 10-50% and (3) strong positive ≥ 50% [10]. For Ki67 any brown nuclear staining, regardless of its intensity was considered to be positive [16,17]. Immunoreactivity was classified as follows: (-) ≤ 5% negative, (+) 6-25 % low proliferation ,(++) 26-50% moderate proliferation and (+++) 51-100% high proliferation of the considered positive cells [18].

All the data of the studied samples were subjected to computerized statistical analysis using SPSS version 19 computer program. Kruskall-Wallis H test was used to compare between the percentages of markers expression among lesion types.

Mann-Whitney U test used after Kruskall-Wallis H test if it is significant to test any significant difference between each two lesions. Spearman's Rank correlation test was used to test the relation between the markers in each lesion type. The positive sign of r value means there is direct relation and vice versa.

RESULTS

The results of present study revealed female predilection in both central and peripheral giant cell granlomma comprising (60%) of (9) cases in each of them. Similarly, in GCT, there was female predilection comprising (53.3 %) of 8 cases as shown in table (1 and 2).

The age range of the patients was 8-52years with a mean of (25.93±13.5) yearsfor C.G.C.G. and age range of 3-75years with a mean of (41.6±23.5) yearsfor peripheral giant cell granuloma Whereas for patients with giant cell tumor the age range was 2-73 years with a mean of (32.5±17.5) years. As demonstrated in table (1 and 2).

Considering site distribution, giant cell granuloma lesions were distributed between upper and lower jaw as follow: C.G.C.G. presented in maxilla in 20% (3 cases) and in the mandible80% (12 cases), P.G.C.G occurred in maxilla in 46.7% (7 cases) and in the mandible 53.3% (8 cases). Whereas, Giant cell tumor cases were distributed among various body regions beginning with head area andRadius bone 33.33% (5 cases) for each of them followed by Femur bone 26.66% (4 cases) and Tibia bone 6.7% (1 case), as shown in table (1 and 2).

Table 1: The demographic and clinical description of 15 patients with central giant cell granuloma and 15 patients with peripheral giant cell granuloma

Lesion type	Site		Sex		Age			
	Mand.	Maxilla	Male	Female	Mean	S.D.	Min.	Max.
CGCG	12 (80%)	3 (20%)	6 (40%)	9 (60%)	25.93	13.6	8	52
PGCG	8 (53.3%)	7 (46.7%)	6 (40%)	9 (60%)	41.6	23.5	3	75

Table 2: The demographic and clinical description of 15patients with Giant cell Tumor

Sex		Age				Site			
Male	Female	Mean	SD	Min.	Max.	Tibia	Femur	Radius	Head
7 (46.7%)	8 (53.3 %)	32.5	17.5	2	73	1 (6.7%)	4 (26.7%)	5 (33.3%)	5 (33.3%)

Assessment of the immunohistochemical expression of WWOX and KI67 Mabs

Positive WWOX Immunostaining was detected as brown cytoplasmic or cytoplasmic with nuclear expression, mostly in multinucleated giant cells and some of mononuclear cells of CGCG, PGCG and GCT **(Fig. 1-3).**

Analysis ofimmunohistochemicalexpression of WWOX Ab. in CGCG,PGCG and GCT revealed positive expression in 12 cases (80%)of CGCL , 14 cases (93.3 %)of PGCL and12(80%) of GCT studied cases .Results revealed predominance of score 3 i.e strong positive expression in bothCGCG and PGCG with 10 cases (66.7 %) of CGCG and 12 cases (80%) of PGCG respectively ,whereas in GCT , positive cases of WWOX expression revealed equal distribution between strong and weak expression scores with 6 cases (40 %) for each one as shown in the table(3).

Table 3: Immunohistochemical expression of WWOX in all giant cell lesions

Lesions	I	II	III	Total
C.G.C.G.	3 (20%)	2 (13.3%)	10 (66.7%)	15(100%)
P.G.C.G.	1 (6.7%)	2 (13.3%)	12 (80%)	15(100%)
G.C.T.	3 (20%)	6 (40%)	6 (40%)	15(100%)

Positive KI67 Immunostaining was detected as brown nuclear expression of stromal cells ofCGCG, PGCG and GCT (Fig. 4-6).

Analysis of immunohistochemicalexpression of Ki67 Ab. in CGCG,PGCG and GCT revealed positive expression in 12 cases (80%) of CGCL , 13cases (86.7 %)of PGCL and10(66.7%) of GCT studied cases .Positive casesrevealed predominance of high proliferative expression scorein bothCGCG and PGCG with 9 cases (60%) of CGCG and 10 cases (66.7%) of PGCG respectively ,whereas in GCT, results revealed low proliferation score in 5 cases (33.3 %), 3 cases (20%) with moderate proliferation score and the remaining 2 cases (13.3%) with strong expression scoreas shown in the table(4).
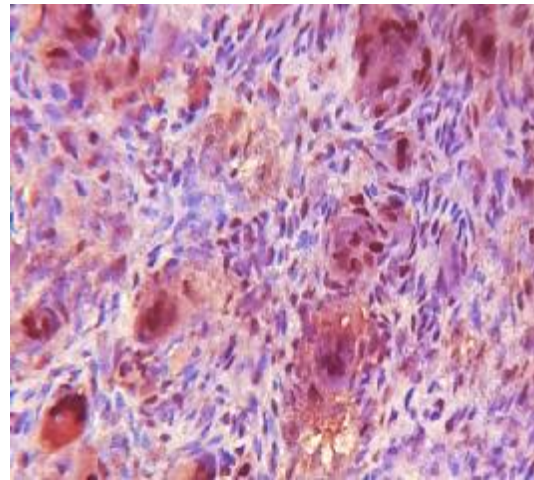
Table 4: Immunohistochemical expression of KI67 in all giant cell lesions

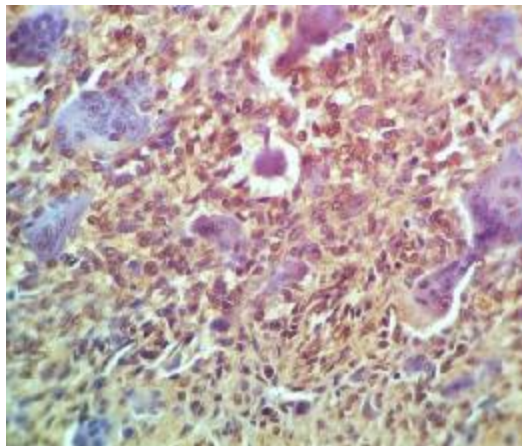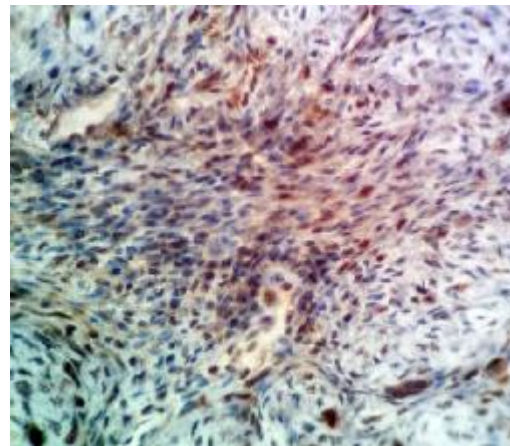| Lesions	-ve	I	II	III
C.G.C.G.	3 (20%)	1 (6.7%)	2 (13.3%)	9 (60%)
P.G.C.G.	2 (13.3%)	1 (6.7%)	2 (13.3%)	10 (66.7%)
G.C.T.	5 (33.3%)	5 (33.3%)	3 (20%)	2(13.3%)
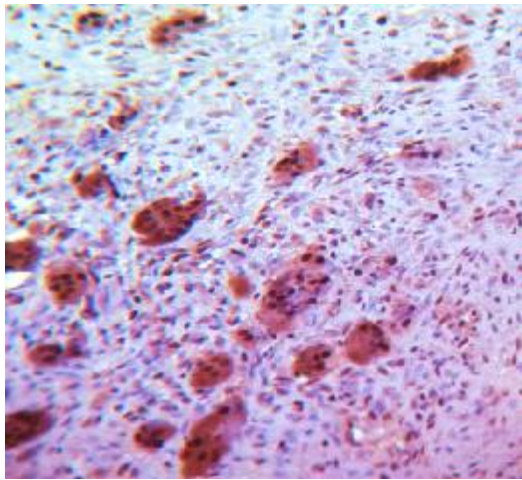
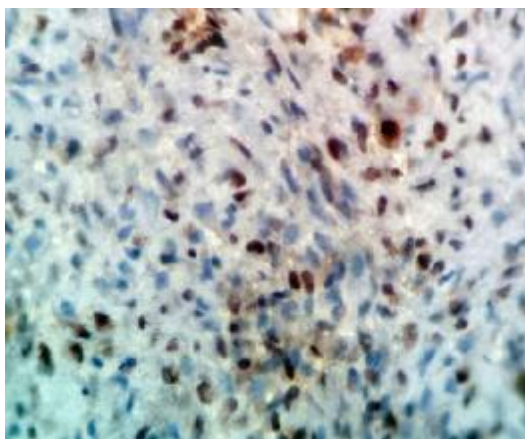**Figure 1: Positive WWOX immunostaining in CGCG(X40)**

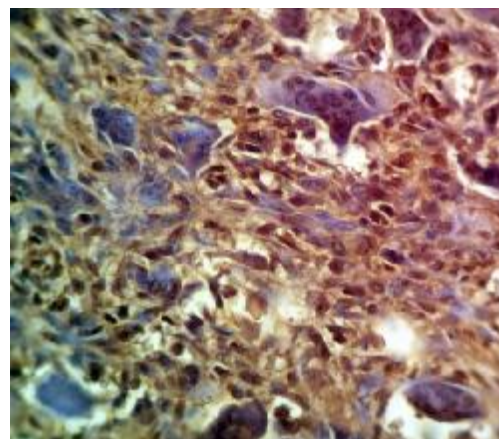**Figure2: Positive WWOX immunostainig in PGCG(X40)**

Figure 3: Positive WWOX immunostaining in GCT(X40)

Figure 4: Positive Ki67 immunostaining in CGCG (X40)

Figure 5: Positive Ki67 immunostaining in PGCG (X40)

Figure 6: Positive Ki67 immunostaining in GCT(X40)

Comparison the percentages of Ki67 and Wwox expression among different studied giant lesion types

Statistical analysis using Kruskal Wallis and Mann Whitney tests revealed that, there is a highly significant difference in the expression of Ki67 between the high PGCG mean percentage (65%) &low GCT mean percentage (25.67%) withp value =0.006 .On the other hand ,non significant difference was found in WWOX expression amongthe studied giant lesions (p=0.060) (Table 5 and 6)

Table 5: Comparison the percentages of Ki67 and Wwox markers among the lesions

Markers	Lesions	Descriptive statistics							Comparison		
		N	Median	Mean	S.D.	Min.	Max.	Mean Rank	Kruskall-Wallis H test	d.f.	p-value
Ki67	**CGC**	15	60	51.67	33.31	0	90	24.27	10.39	2	0.006 (HS)
	PGC	15	80	65	33.49	0	95	29.97			
	GCT	15	20	25.67	25.06	0	75	14.77			
Wwox	**CGC**	15	80	60	33.91	0	90	24.37	5.64	2	0.060 (NS)
	PGC	15	80	69.33	24.92	0	90	27.83			
	GCT	15	50	45	31.11	0	85	16.80			

Table 6: Mann-Whitney U test after Kruskall-Wallis H test for Ki67

Lesions	Mean Rank	Mann-Whitney U test	Z-test	p-value
CGC	13.27	79	-1.39	0.162 (NS)
PGC	17.73			
CGC	19	60	-2.19	0.028 (S)
GCT	12			
PGC	20.23	41	-2.97	0.003 (HS)
GCT	10.77			

Correlation between thepercentages of Ki67 and WWox in the studied cell lesions:

Results of present study and according to spearman's test correlation revealed non-significant correlation between the expression of WWOXand KI67 in CGCG, PGCG and GCT studied cases (Table 7-9).

Table7: Relation between the percentages of Ki67 and WWOX in CGCG

Markers		WWOX
Ki67	**R**	0.488
	p-value	0.065 (NS)

Table 8: Relation between the percentages of Ki67 and WWOX in PGCG

Markers		WWOX
Ki67	**R**	0.315
	p-value	0.253 (NS)

Table 9: Relation between the percentages of Ki67 and WWOX in GCT

Markers		WWOX
Ki67	**R**	0.339
	p-value	0.216 (NS)

DISCUSSION

Giant cell lesions of the jaw and GCT of long bones have a distinct clinical behavior. Both lesions are characterized histologically by multinucleated giant cells in a background of ovoid to spindle-shaped mesenchymal cells. There is a basic question whether both lesions are separate entities or variants of the same disease, [18] and if biological behavior differences are supported by a distinct pattern of certain markers proteins expression or not. Therefore this study was conducted in an attempt to assess the expression of WWOX tumor suppressor gene and proliferative marker Ki67 in giant cell lesions of the jaw bones in comparison to the giant cell tumor of long bones and to correlate their expression with each other in each studied lesion

to explain its possible role in the biological behavior of giant cell lesions and tumor.

The WWOX gene is a recently cloned tumor suppressor gene that spans the FRA16D fragile region. WWOX protein contains two WW domains that are generally known to mediate protein-protein interaction [13]. The subcellular localization of WWOX has been a controversial issue among the different research groups. Numerous immunohistochemical studies have shown that WWOX is a cytoplasmic protein both in normal and neoplastic tissues [20-25]. Other laboratories have reported that WWOX localizes in mitochondria and nuclei of some cells [26]. In the present study, both cytoplasmic and cytoplasmic/nuclear staining pattern was considered positive in both mononuclear and multinucleated giant cells.

Results revealed strong positive WWOX expression in majority of PGCG and CGCG studied cases, mostly in the giant cells; this finding is supported by results of previous study [27]. These findings support what previously reported that WWOX has an important role in apoptosis since it is mostly expressed in giant cells which have been shown to be the main source of this apoptotic event [26]. Concerninig expression in GCT ,and up to my knowledge this is the first study that attempt to compare WWOX expression in giant cell lesions of the jaw bones and giant cell tumor of long bones.The present finding showed that the majority of GCT cases showed positive expressionwith non-significant difference obtained in WWOX expression amongCGCG, PGCG and GCT studied cases.This finding is in accordance with previous study conducted using other tumor suppressor gene [28] which supports the theory that these lesions are a spectrum of disease rather than different entities. On other hand the present findings indicate that WWOXcould not be used to explain the differences between the giant cell lesions of the jaws and GCT of the long bones.

The Ki-67 antigen is a human nuclear protein used as a marker for cellular proliferation [15] Ki-67 antigen is expressed during the G1, S, G2 and M phases of the cell cycle within the nucleus but is not expressed during the G0 (resting) phase, and thus it is a widely accepted proliferation marker and is useful in predicting the development of human neoplasm [14].

Although the biological behavior is not only reflected by the proliferation index by tumor cells, but still it represents a clue on tumor activity .The results of previous study showed greaterKi-67 immunoreactivity in PGCL compared to CGCL[29]. Similar results obtained in the present study. Additionally, CGCG and PGCG had a higher proliferative activity than GCT with a highly significant difference in Ki67 expression was found between CGG, PGCG and giant cell tumor. Similar results obtained in previous studies [29-31]. However, Souza, et al. stated that the differences observed in proliferative activity do not explain the different biological behavior of CGCG and GCT. They emphasized that since CGCG and GCT occur in different sites, it is difficult to compare accurately their biological evolution [28]. They suggested that CGCG and GCT could represent variants of the same disease.

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الخلاصة

الخلفية :ان آفة الخلايا العملاقةالطرفيةوآفة الخلايا العملاقة المركزية للفكين لهاسلوكسريري واضح .ان ورم الخلايا العملاقة هومن الاورام الحميدة المحددة العدوانية يصيب العظام الطويلة وتتميز كلا الافات تشريحيا من الخلايا العملاقة المتعددة النوى في خلفية من الخلايا البيضوية الى مغزلية الشكل من خلايا اللحمة المتوسطة.ان جين (WWOX) يقع ضمن منطقة(16q23.2–16q23.1) وهي المنطقة التي تضم الموقع البشري الهش الاكثر شيوعا.ان بروتين (Ki-67) هو بروتين نووي مقترن بعملية تكاثر الخلايا وضروري لها .ان هذا البروتين موجود اثناء كل الاطوار الفعالة من دورة الخلية ولكنه غائب عن الخلايا الساكنة. هدفت هذه الدراسة الى تقييم ومقارنة الاظهار الكيميائي النسيجي المناعي للجين المثبط للاورام (WWOX) ومعلم التكاثر (ki67) في آفات الخلايا العملاقة للفكين والعظام الطويلة.

المواد والطرق : تم تضمين خمس واربعين عينة نسيجية استرجاعيةمطمورة بالبارافين من آفات الخلايا العملاقة للفكين والعظام الطويلة في هذه الدراسة .تم صبغ المقاطع النسيجية لهذه العينات باستخدام الصبغات النسيجية المناعية بمضادات ال(WWOX) وال(ki67).

النتائج:وجد الاظهار الايجابي لل (WWOX) في 12حالة (80%) ,14حالة (93.3%) و12 حالة(80%) من الحالات المدروسة من ال (CGCG),(PGCG) و(GCT) على التوالي.ووجد الاظهار الايجابي لل (Ki67) في 12 حالة (80%), 13 حالة (86.7%) و 10 حالات من الحالات المدروسة من (CGCG) , (PGCG)و(GCT) على التوالي مع تسجيل مؤشر عالي للتكاثر في (PGCG).وجد فرق كبير للغاية بين الحالات المدروسة في اظهار ال (Ki67) مع عدم وجود فرق بينها في درجة اظهار ال (WWOX).تم العثور على علاقة غير كبيرة بين ال (WWOX) و (Ki67) في مختلف آفات الخلايا العملاقة المدروسة.

الاستنتاجات:تتشابه الظهور الكيميائي النسيجي المناعي لل(WWOX) و(Ki67) في آفات الخلايا العملاقة في الفكين والعظام الطويلة مع وجود علاقة غير معنوية بينهما في مختلف الحالات المدروسة الامر الذي يدل على ان هذه الآفات قد تكوننفس المرض ولكن بحالات سريرية مختلفة**.**