

Original Research Article

Immunohistochemical expression of CD163, vimentin, and nerve growth factor receptor in giant cell fibroma of oral mucosa (A cross-sectional study)

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Abstract – Objectives: Giant cell fibroma (GCF) is a rare oral mucosal lesion characterized by the presence of giant and stellate cells within its fibrous stroma. This study aimed to investigate the cellular origin and immunophenotypic profile of GCF, with particular emphasis on evaluating histiocytic and possible neural differentiation using vimentin, CD163, and nerve growth factor receptor (p75NTR). **Material and methods:** A total of 61 paraffin-embedded tissue sections of GCF were obtained from the archives at the College of Dentistry, University of Baghdad between 2010-2024 and stained immunohistochemically for vimentin, CD163, and p75NTR. **Results:** Vimentin and CD163 showed strong positivity in stromal and giant cells, with an average of 73.75% and 59.2%, respectively. However, a cytoplasmic staining of p75NTR was observed in all patients without membranous reactivity. **Conclusion:** The findings suggest a fibro-histiocytic origin of GCF with limited evidence of neural differentiation, which requires further investigation

Introduction

Giant cell fibroma (GCF) is an oral soft tissue lesion with distinctive clinicopathological features [1]. Weathers and Callihan first described GCF as a separate entity among fibrous hyperplastic soft tissue lesions in 1974 when 108 out of 2000 fibrous hyperplasia specimens met the GCF criteria [2]. Unlike traumatic fibroma, GCF is not associated with chronic irritation [3].

Clinically, GCF is characterized by an asymptomatic nodular mass of <1 cm, most frequently occurring in the gingiva [4]. The surface may be smooth, lobulated, or papillary; thus, the lesion clinically appears to be a papilloma [5]. It almost always occurs before the age of 30 yr, with a slight female predilection [6]. Histologically, the surface is stratified into squamous epithelium, covering loose or dense fibrous stroma with numerous large stellate mono-, bi-, or multinucleated giant cells, well-demarcated cytoplasm, dendritic processes, and surrounded by an artifactual space or separation of collagen fibers from the cell boundaries [7].

These multinucleated giant cells are also found in other fibrous lesions such as ungual fibroma, acral angiofibroma, cutaneous giant cell fibroblastoma, and cutaneous collagenoma [8].

Despite previous discussions on GCF, the nature, phenotypic characterization, and immune profile of GCF remain elusive [9] and a few immunohistochemical studies focused on exploring the origin of the giant cells in GCF was performed since it has low incidence, prevalence, and indolent behavior [10]. Previous studies have generally pointed to a mononuclear fibroblastic origin and a fibroblastic phenotype. One cannot completely rule out the idea that some of these giant cells are derived from primitive mesenchymal tissues that may have neural or histiocytic differentiation [5–10]. Despite multiple studies, the exact cellular origin of multinucleated giant cells remains controversial. This study aims to investigate the cellular origin of multinucleated giant cells in GCF by assessing mesenchymal, histiocytic, and neural markers.

Vimentin, an intermediate filament protein, is usually associated with primitive mesenchymal malignancies [11].

NGFR (p75NTR) a transmembrane protein in the tumor necrosis factor receptor family, is widely used as a diagnostic for neural origin oral cancers, this marker was included to explore possible neural differentiation based on its expression in neural crest-derived cells [12]. CD163 a glycoprotein from the scavenger receptor cysteine-rich family, is currently the most specific marker for monocytes and macrophages in diagnostic applications due to its higher specificity compared to CD68, which may show cross-reactivity with fibroblasts [13].

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Material and methods

Sample

The sample size was calculated using G power software ver. 3.1.9.7. The study power was set to 80%, alpha error probability = 0.05 (2-tailed), and correlation ρ H1 = 0.35 (moderate). The total sample size was 61 [14].

A total of 61 formalin-fixed paraffin-embedded tissue blocks of GCF, along with clinical data (age, sex, and site), were obtained from the archives of the oral pathology laboratory at the College of Dentistry, University of Baghdad, from 2010 to 2024. After obtaining approval from the ethical committee (No.004718), immunohistochemical staining was performed using vimentin, CD163, and p75NTR antibodies. The study was conducted according to SRT0BE Guidelines.

Immunohistochemistry

For the preparation of immunohistochemical analysis, serial slices of four-micron tissue sections were taken from each tissue block. The staining process was performed based on instructions provided by the manufacturer. Three primary antibodies manufactured by Abcam (Cambridge, UK) were used as an anti-vimentin antibody (ab224829), anti-CD163 antibody (ab87099), and anti-P75(NGFR) (ab227509). The antibodies were used at dilutions specified in the modified manufacturer's datasheets.

Detection was performed using the Mouse and Rabbit Specific HRP/DAB Detection IHC kit (Abcam, ab236466; 15 ml), which was utilized for detecting all primary antibodies. Negative controls were carried out on consecutive sections with the omission of the primary antibody, resulting in no detectable staining.

All spindle and giant cells with cytoplasmic vimentin, membranous and cytoplasmic CD163, and membranous NGFR (p75NTR) expressions were considered positive based on the manufacturer data sheets of each marker.

An immunostaining assessment was performed using a light microscope (Olympus CH). All slides were initially scanned by two experienced pathologists at low power (X10) to select five representative fields, which were then visualized and scored using an X40 objective. A mean positive percentage was recorded. The percentage of positive cells was scored semi-quantitatively, as illustrated in Figure 1 and Table I.

Statistical analysis

The Statistical Package for Social Sciences version 26 (IBM, USA) was used for all statistical analyses. The descriptive analysis for total immunopositive cells and positive giant cells summarized using mean, SD and 95% confidence interval. The vimentin and CD163 correlations was calculated using Pearson's correlation test Since the data normally distributed. The significance level of $p < 0.05$ was considered statistically significant.

Results

Expression of vimentin

Cytoplasmic vimentin expression was positive in all patients as shown in Figure 2 with a mean of 73.75% (SD = 11.91) of lesional cells and 51.08% (SD = 25.52) of giant cells and scored 4 for all patients (Figs. 1A and 1B). Despite the uniform positivity, no statistically significant correlation was identified between the proportion of total immunopositive cells and the number of positive giant cells (Fig. 1C), suggesting that vimentin expression reflects a generalized stromal characteristic rather than being specifically associated with the formation or distribution of multinucleated giant cells.

Expression of CD 163

Membranous and cytoplasmic CD163 expressions were positive as shown in Figure 3 with a mean of 59.2% (SD = 12.82) of the lesional cell and 46.07% (SD = 20.27) of giant cells; however, 68.9% of patients scored 2 and 31.1% scored 1. A statistically significant positive correlation was observed between the percentage of total immunopositive cells and the number of positive giant cells for CD163 as detected in Figure 1D, suggesting that histiocytic differentiation may play a role in the formation or accumulation of multinucleated giant cells within GCF.

Furthermore, a moderate but statistically significant positive correlation was identified between vimentin and CD163 expression levels ($r = 0.391$, $p = 0.002$), supporting the concept of overlapping mesenchymal and histiocytic phenotypic features in the lesional cells.

Expression of NGFR (p75NTR)

In all patients, a remarkable positive cytoplasmic expression of NGFR (p75NTR) was observed, as depicted in Figure 4. Based on the manufacturer's datasheets and previously established interpretation criteria, NGFR expression is considered positive only when membranous staining is present. Therefore, the observed cytoplasmic reactivity in this study was interpreted as negative for true neural differentiation.

This pattern may reflect non-specific cytoplasmic accumulation or intracellular sequestration of the protein rather than functional receptor expression, and thus should be interpreted with caution.

Discussion

The assessment of the GCF immune profile in our study revealed a strong cytoplasmic positivity for vimentin. These findings align with that of previous studies suggesting a fibroblastic differentiation [9, 18–21]. However, vimentin is notably not a cell-type-specific marker for multinucleated giant cells, leaving the histogenesis of these cells elusive

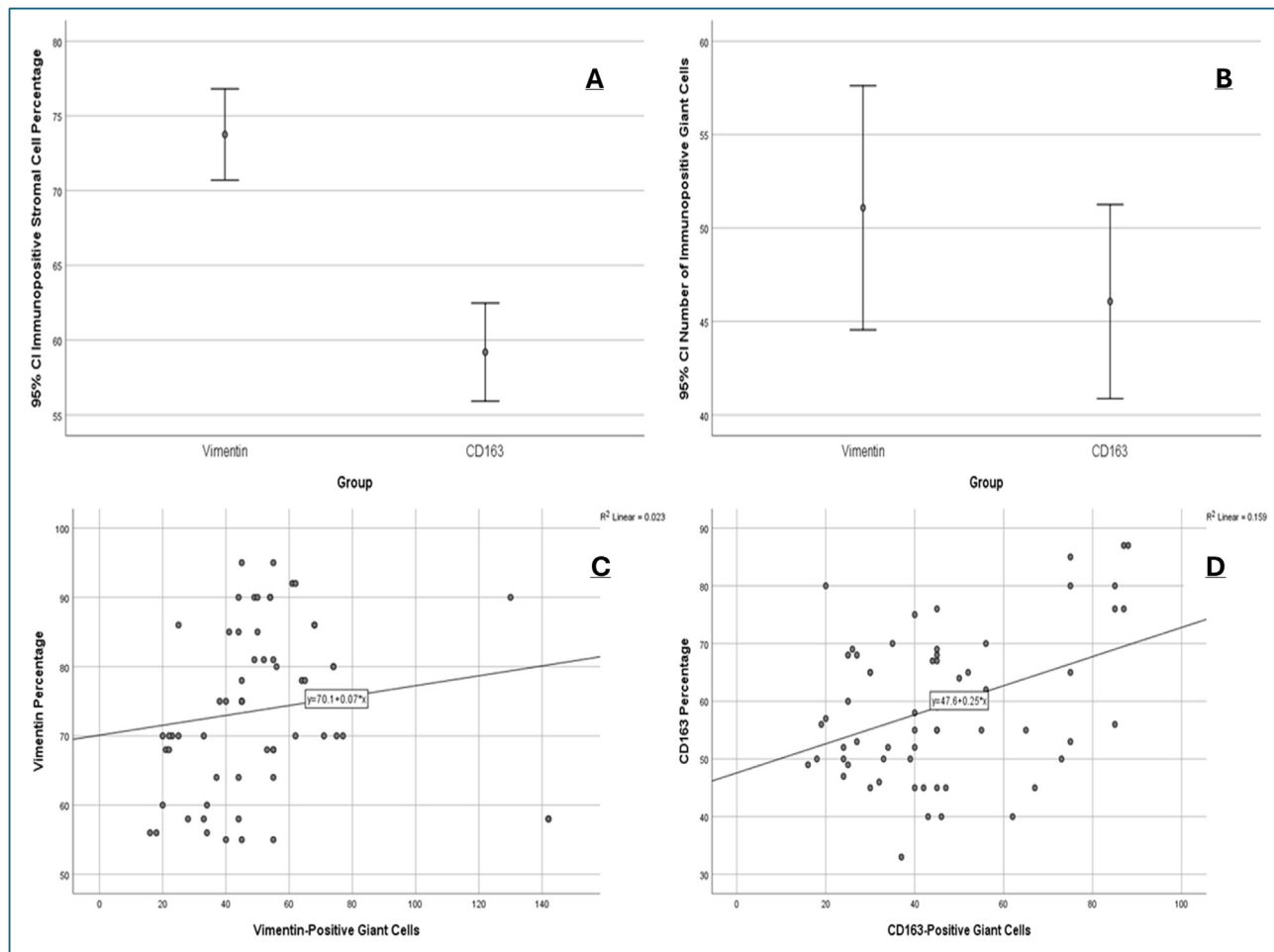


Fig. 1. A: Mean and 95% confidence interval for total immunopositive stromal cells. B: Mean and 95% confidence for the number of immunopositive giant cells. C: Vimentin correlation. D: CD163 correlation.

Table I. Scoring system of immunohistochemical markers.

IHC marker	0 score	+1 score	+2 score	+3 score	+4 score
Vimentin [15]	Nonreactive	Scattered spottystaining	up to 25%	25%-50%	>50%
CD 163 [16]	<10%	11%–50%	>50%		
NGFR(P75) [17]	0–1%	>1%–10%	>10%–25%	>25%–75%	>75%–100%

[20–22]. Vimentin positivity confirms the mesenchymal nature of the lesional cells; however, due to its lack of specificity, it cannot be considered definitive evidence of fibroblastic histogenesis., which is consistent with the findings of Regzie *et al.* [15].

The potential for histiocytic differentiation in GCF was explored by assessing the CD163 expression, a highly specific marker for histiocytic lineage differentiation (monocyte and macrophage) in the diagnostic use [17]. The specificity of CD163 was supported by the result of the study done by Lau *et al.*, (2004) who demonstrated that CD163 is a highly specific marker for cells of monocyte/macrophage lineage, which seems

suitable for routine use in paraffin-embedded tissue samples and offers an alternative to CD68 antibodies for identifying cells of monocyte/macrophage derivation in normal and neoplastic conditions [16]. The focus on macrophage-related markers in this study was intentional, as previous literature has primarily suggested a possible macrophage or fibroblastic origin of multinucleated giant cells, rather than a dendritic cell lineage.

The positive CD163 expression in all patients supports the concept proposed by Regzie *et al.* in 1987 [2-], whereas contradicting studies used less specific histiocytic markers such as factor XIIIa [9, 18] and CD 68 [18].

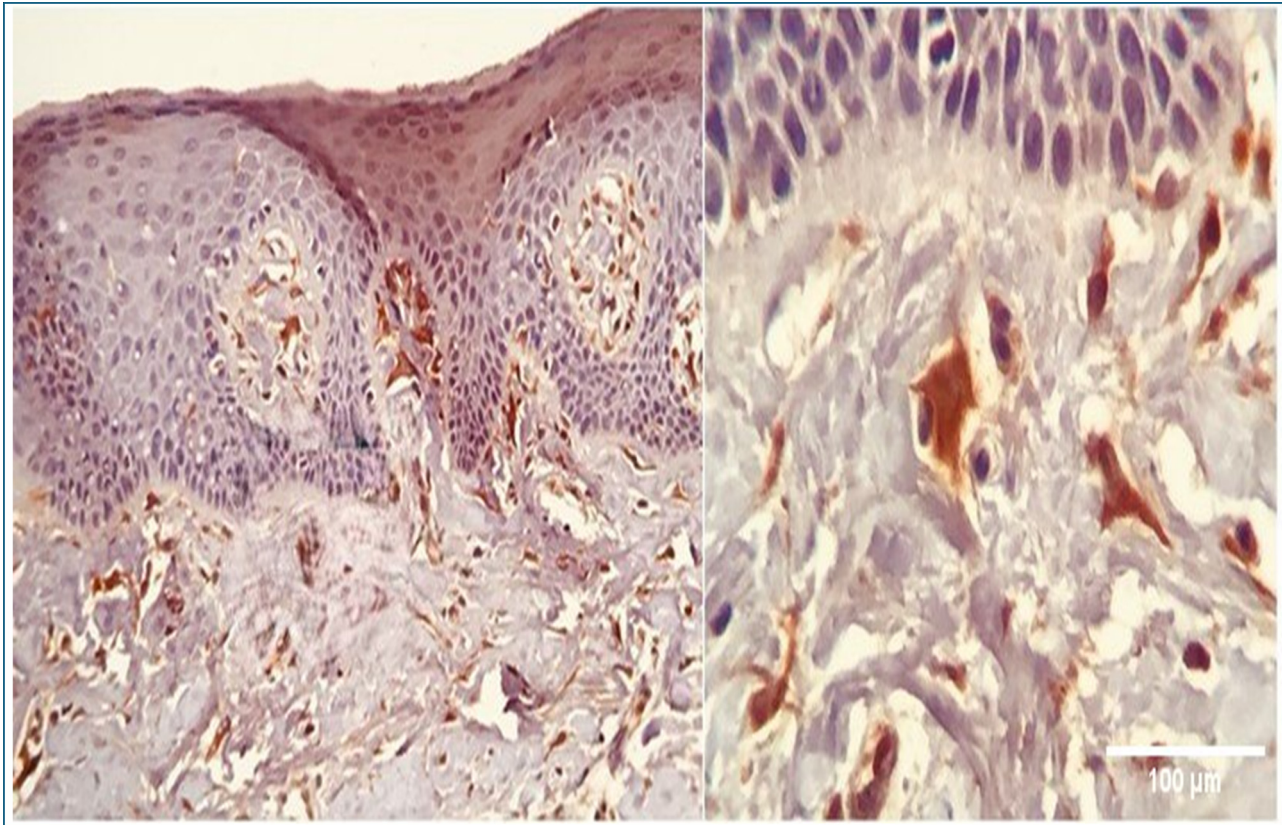


Fig. 2. Immunohistochemical expression of vimentin in GCF showing strong cytoplasmic positivity in giant and surrounding spindle stromal cells. (scale bar length: 100 micron).

Remarkably, our study reveals a statistically significant positive correlation between vimentin and CD163 expression, suggesting overlapping phenotypic features rather than definitive evidence of histogenesis. Further, the positive correlation between the CD163 expression and the number of positive giant cells suggests a predominance of histiocytic rather than fibrous or primitive mesenchymal characteristics.

Several authors have discussed the potential neural or neuroectodermal differentiation of GCF using markers such as S-100, NSE, GFAP, and neurofilament [9, 15–19, 21].

In our study, the nerve growth factor receptor (p75NTR) was used as a more specific marker that labels both neural and epithelial structures. Intense staining of neural structures in the superficial and deep lamina propria was observed with NGFR (p75) [15]. The data sheets and prior literature on this marker in other lesions [23] reported that NGFR antibody is considered positive only when it exhibits membranous reactivity. In our study, all patients with GCF exhibited clear cytoplasmic positivity for NGFR (p75NTR). This could be due to sequestration from the membrane. The nonspecific sequestration of soluble proteins by other cells of a different lineage or the cell interstitium is a common problem in thyroglobulin detection, which can also be observed with myoglobin, glial fibrillary acidic protein, and other cellular proteins [24–26]. Although it

cannot be definitively classified as positive, this finding is noteworthy and requires further validation before it can be considered as a marker for this unique lesion, however, the study of higher number of GCF cases and use of wider range of mesenchymal and histiocytic markers is recommended to improve these results.

From the clinical point of view, recent studies are supportive of a neoplastic nature of GCF rather than a reactive one, especially considering the p53 and tenascin expression, and this should implicate an autonomous but limited growth capacity of GCF. As a benign tumor [10] although fibrous overgrowths of the oral cavity are benign diseases, a histological analysis of the tissue is required to rule out the possibility of malignant alterations. These benign growths may continue to grow in size following local irritation or chronic trauma unless the source of irritation is removed, or the lesion is completely excised. Early diagnosis was required in many reported cases where the patient appeared to be of a large, unusual size and was at a higher risk of developing oral cancer, such as smokers and older age patients. Early removal of this lesion reduced the likelihood of more complex surgical intervention at a later stage [4, 27].

Acknowledging the retrospective nature of this study, our focus was narrowed to biopsy-proven GCF lesions. The relative rarity of these lesions inherently limited the scope for broader

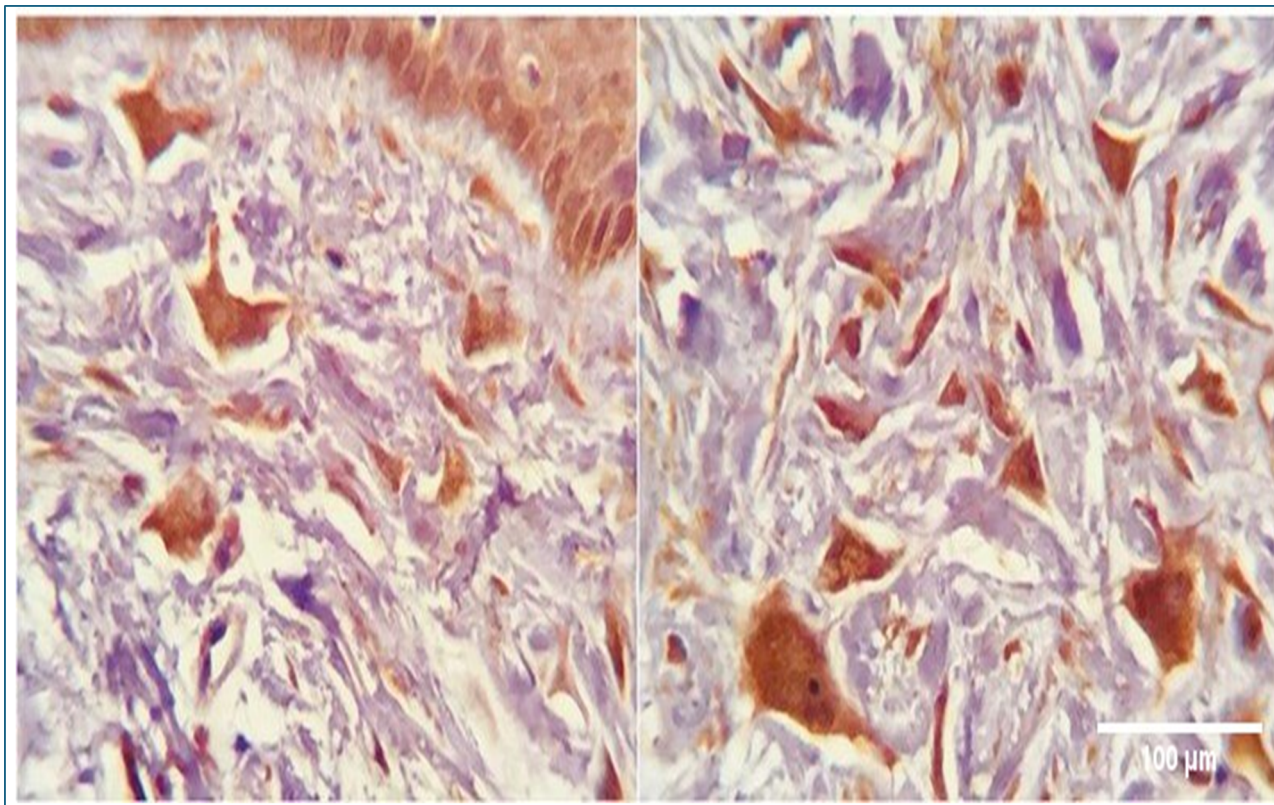


Fig. 3. Positive cytoplasmic and membranous expressions of the CD163 immunohistochemical marker in stromal and multinucleated giant cells of GCF. (scale bar length: 100 micron).

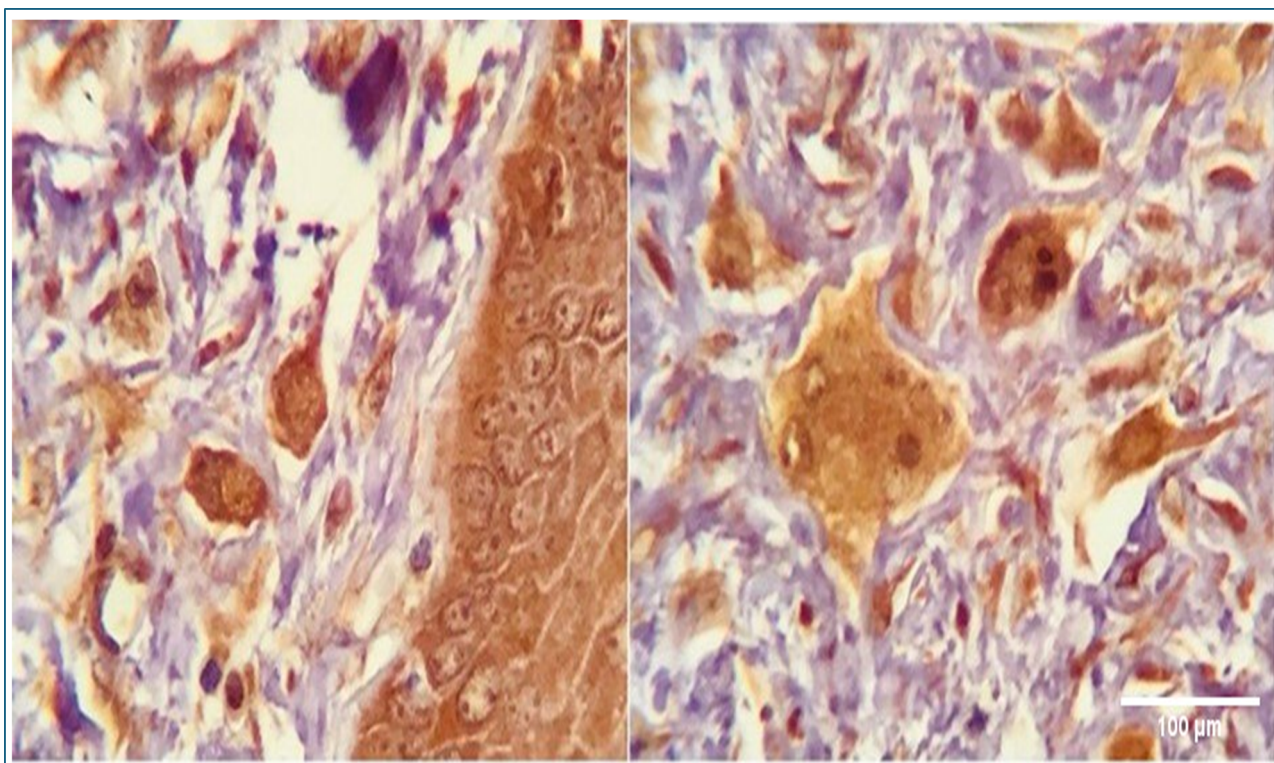


Fig. 4. Immunohistochemical expression of NGFR showing the cytoplasmic expression in giant and surrounding spindle cells. (scale bar length: 100 micron).

statistical analyses. It is posited that future studies, benefiting from multicenter data pooling, with inclusion of more markers such as CD68 or dendritic cell markers (*e.g.*, DC-SIGN or CD207) could offer a more precise delineation of the pathogenesis, immunoprofile, clinical Presentation and treatment measures thus enriching the existing body of knowledge on GCF.

In conclusion, this study proved that giant cell fibroma is more favorable of fibro histiocytic origin rather than fibrous origin.

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Conflicts of interest

The authors declare that they have no conflict of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to ethical and privacy restrictions related to patient information.

Author contribution statement

Fatimah J. Ismael: Conceptualization, Methodology, Writing original draft
Bashar H. abdullah: Visualization, Investigation and Supervision.
Jose Luis Tapia: Writing- Reviewing and Editing.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University of Baghdad, College of Dentistry, Iraq (number 652622).

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