J. Oral Diagn 2024;09:e263

ORIGINAL ARTICLE

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# Immunohistochemical expression of p53, ki-67, tenascin, and fibronectin in giant cell fibroma and traumatic fibroma of the oral mucosa

## Abstract:

**Objective:** This study aimed to compare the immunoexpression of p53, ki-67, tenascin, and fibronectin between giant cell fibroma (GCF) and traumatic fibroma (TF), in order to explore a benign neoplastic or a reactive nature of GCF. **Methods:** A cross-sectional study was conducted. Samples of GCF and TF were retrieved from the files of Oral Pathology Service, matched by site and size. Immunohistochemistry for p53, ki-67, tenascin, and fibronectin was evaluated in the superficial and deep regions of the lesions using the Image J Software. The number of positive cells was determined for p53 and ki-67, and the positive area was established for tenascin and fibronectin. Statistical analysis was performed with Mann-Whitney and independent t-tests ($p \leq 0.05$). **Results:** Comparing to TF, GCF showed higher expression of p53 protein in superficial ($p=0.009$) and deep regions ($p=0.027$), as well as higher tenascin expression in deep regions ($p=0.000$). Ki-67 and fibronectin immunoexpression did not differ between GCF and TF ($p>0.05$). **Conclusion:** The results of the present study seem supportive of a benign neoplastic nature of GCF, rather than a reactive one, especially considering the p53 and tenascin expression. Further studies with larger samples and broader markers should confirm this hypothesis.

**Keywords:** Giant cell fibroma; Immunohistochemistry; Ki-67; P53; Tenascin.

## INTRODUCTION

Giant cell fibroma (GCF) is a fibrous lesion first described by Weathers and Callihan in 1974[1]. It commonly affects the oral cavity of Caucasian patients in the first three decades of life, appearing as an asymptomatic, pink, fibrous nodule, of no more than 10 mm[2]. On histopathology, GCF shows mono-, bi-, or multinucleate spindle-shaped or stellate giant cells of fibroblastic origin, usually found in the subepithelial connective tissue[1].

**Statement of Clinical Significance**
The present study favors a benign neoplastic nature of oral giant cell fibroma, though additional research is needed to definitively determine the nature of this lesion. This should implicate an autonomous but limited growth capacity of oral giant cell fibroma, which should be treated by conservative surgical excision, with no recurrences expected.

Traumatic fibroma (TF) is a well-recognized reactive lesion caused by chronic trauma, such as a biting habit, which induces fibroblasts to synthesize and accumulate collagen fibers[3]. In addition to the similar histogenesis with GCF, it may resemble this condition from the clinical point of view. However, both differ primarily in etiological and microscopic factors. Microscopically, fibroblasts in GCF appear as giant, stellate, and often binucleated cells within a delicate collagen background. On the other hand, TF shows spindle-shaped fibroblasts dispersed in a collagen matrix composed of large and dense fibers.

Research on the GCF has been focused on the characterization and investigation of the giant cells'

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Received on September 10, 2024. Accepted on October 16, 2024.
https://doi.org/10.5327/2525-5711.263

origin[3-7], while the etiology of the GCF remains unestablished. Some authors recognize it as a reactive non-neoplastic condition and others as a benign neoplasm, mainly because of the lack of association with a causative chronic irritative factor[3-7]. Few studies evaluated immunohistochemical markers that could help in understanding GCF etiopathogenesis.

p53 is a cell-cycle regulatory protein that acts as a tumor suppressor, while ki-67 is a nuclear protein broadly used as a proliferation cell marker[8,9]. Tenascin and fibronectin are physiological glycoproteins of the extracellular matrix involved in wound repair and neoplastic processes[10-12]. Tenascin has functions in the dynamics of the extracellular matrix and cell migration, while fibronectin is a structural protein that acts on cell adhesion to collagen fibers[12].

The present study aimed to compare the immunoexpression of p53, ki-67, tenascin, and fibronectin between GCF and TF, in order to explore a possible benign neoplastic or a reactive nature of GCF. This will improve the general understanding of GCF pathogenesis and to correctly classify this entity, providing more accurate epidemiological data on this oral lesion.

## MATERIAL AND METHODS

### Ethical approval

The study was approved by the *Research Ethics Committee of Universidade Federal de Minas Gerais* (certificate number: 15899419.1.0000.5149) and conducted in accordance with the Declaration of Helsinki, assuring the anonymity of the participants.

### Study design and sample selection

This cross-sectional observational study was performed and reported following the STROBE guidelines. Cases with a microscopic diagnosis of GCF were retrieved from the Oral Pathology Service of the School of Dentistry of Universidade Federal de Minas Gerais, Brazil. For this research, only lesions located at the tongue, measuring between 5 and 10 mm, and affecting patients in the 5th and 6th decades of life were included, as these have been the commonest clinical features of GCF[13]. The exclusion criterion was insufficient material in the paraffin block. The H&E slides were reviewed by an experienced oral pathologist (P.C.C.) to diagnosis confirmation. TF samples were retrieved from the same Oral Pathology Service, and were matched by site and size to the GCF group. Thus, all TF included were located at tongue and measured 5 to 10 mm. Information about sex and age of patients of both groups was collected from the biopsy charts, but these variables were not matched between groups.

### Immunohistochemistry

Four-micrometer tissue sections were submitted to immunohistochemistry for p53, ki-67, tenascin, and fibronectin (Table 1).

Samples were deparaffinized with xylol and hydrated with graded ethanol. After antigen retrieval, hydrogen peroxide block and protein block were performed with ready-to-use solutions. Incubation with primary antibody was followed by detection with polymer (CRF Anti-Polyvalent HRP; ScyTek Laboratories, Logan, UT, EUA, code ABZ125) and the reaction was revealed with 3,3′-diaminobenzidine (Spring BioScience, code DAB-999). Hematoxylin was used for counterstaining. Positive controls were: oral squamous cell carcinoma for p53 and fibrous hyperplasia for ki-67 (basal layer of epithelium), tenascin (connective tissue), and fibronectin (connective tissue). Negative control consisted of omission of the primary antibody.

### Immunohistochemistry evaluation

One trained examiner (I.G.O) performed the analyses. Ten 400x magnification hotspot fields were determined in each slide, being five representing superficial interpapilar stroma and five in deep areas of the lesion. These selected fields were photographed using a digital camera attached to an optical microscope (Opticam 600R, LOPT14003). The images were exported to the ImageJ® software for quantification. For p53 and ki-67, positive cells were counted in all photomicrographs, RGB images, using the 'cell counter' plug-in.

**Table 1.** Primary antibodies used for immunohistochemistry.

| Target protein | Clone/manufacturer | Antigen retrieval | Dilution |
|---|---|---|---|
| p53 | Clone DO-7, Dako, Glostrup, Denmark, code M7001 | TRIS-EDTA (pH 9.0) in a 96°C pressure cooker for 30 min | 1:100 |
| Ki-67 | Clone MIB-1; Dako, Glostrup, Denmark, code M7240 | Citric acid solution (pH 6.0) in a 96°C pressure cooker for 30 min | 1:100 |
| Tenascin | Clone DB7; BioGenex, San Ramon, CA, USA | Pepsin (pH 1.8) in a 37°C water bath for 30 min | 1:150 |
| Fibronectin | Polyclonal; Dako, Glostrup, Denmark, code A0245 | Pepsin (pH 1.8) in a 37°C water bath for 30 min | 1:600 |

The total number of positive cells was divided by 5 to establish the mean cell count of the superficial and deep areas, respectively. For tenascin and fibronectin, the percentage of positive area was established. Briefly, the region of interest was delimited in the RGB images and color deconvolution was set for 'H DAB'. The resulting image containing the brown tone was submitted to the 'threshold' tool and the resulting image was used for area measurement. The total positive area was divided by 5 to establish the mean positive area of the superficial and deep areas, respectively.

### Statistical analysis

Statistical analysis was performed using SPSS® software version 26.0 (SPSS, Inc., Chicago, Illinois). Descriptive statistics were done. The Mann-Whitney U test was used to compare the immunoexpression of ki-67, p53, and tenascin between GCF and TF, and the independent t-test was applied to compare the immunoexpression of fibronectin between both lesions. $p \leq 0.05$ were considered indicative of statistical significance.

## RESULTS

Eleven samples of GCF (7 men, 4 women; age range 42-60 years, mean 51 years-old) and eleven TF (7 women, 4 men; age range 11-67 years, mean 47 years-old) were included. All lesions were located at the tongue, were asymptomatic, and were treated by surgical excision (Table 2). Shows the values and comparisons of the immunoexpression of p53, ki-67, tenascin, and fibronectin between GCF and TF. Figure 1, illustrates a case of GCF and Figure 2, a case of TF. Comparing to TF, GCF showed higher expression of p53 protein in

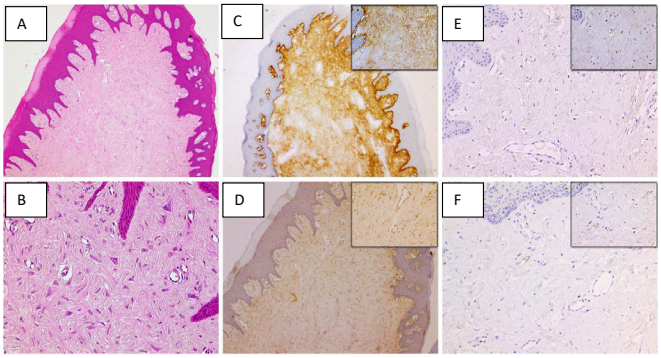


**Figure 1.** Giant cell fibroma. A, B: Large, stellate, and some multinucleated cells within a loose collagen stroma (H&E. 40x and 400x). C: Tenascin diffusely expressed in the stroma. This case was the one with the highest tenascin expression. Other cases showed an evident vascular-associated pattern (immunoperoxidase. 40x, insight 400x). D: Fibronectin diffusely expressed in the stroma (immunoperoxidase. 40x, insight 400x). E: p53 expression in stellate cells (immunoperoxidase. 200x, insight 400x). F: Ki-67 negativity (immunoperoxidase. 200x, insight 400x).

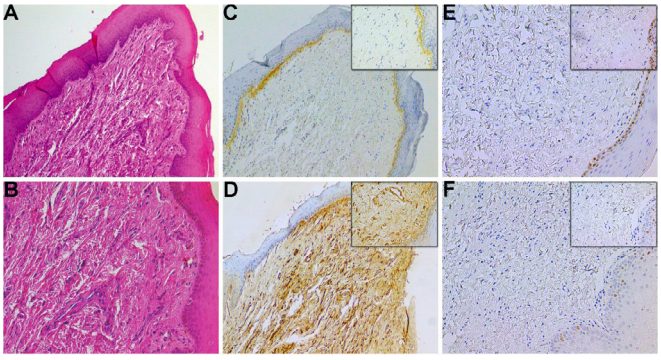


**Figure 2.** Traumatic fibroma. A, B: Small, elongated fibroblasts within a dense collagen stroma (H&E. 100x and 400x). C: Tenascin expressed in the superficial lamina propria, along the basement membrane (immunoperoxidase. 100x, insight 400x). D: Fibronectin diffusely expressed in the stroma (immunoperoxidase. 100x, insight 400x). E: p53 negativity (immunoperoxidase. 200x, insight 400x). F: Ki-67 negativity (immunoperoxidase. 200x, insight 400x).

**Table 2.** Comparative immunoexpression of p53, ki-67, tenascin, and fibronectin between giant cell fibroma (n=11) and traumatic fibroma (n=11) of the oral mucosa.

| Variables | Giant cell fibroma | | | | Traumatic fibroma | | | | p-value |
|---|---|---|---|---|---|---|---|---|---|
| | Median | Min | Max | Mean/SD | Median | Min | Max | Mean/SD | |
| p53 superficial* | 4 | 0 | 20 | 7.18/7.040 | 1 | 0 | 10 | 1.73/2.867 | **0.009**‡,§ |
| p53 deep* | 4 | 0 | 10 | 3.91/3.270 | 0 | 0 | 8 | 1.09/2.343 | **0.027**‡,§ |
| ki-67 superficial* | 0 | 0 | 2 | 0.36/0.674 | 0 | 0 | 3 | 0.36/0.924 | 0.687§ |
| ki-67 deep* | 0 | 0 | 2 | 0.27/0.647 | 0 | 0 | 2 | 0.27/0.647 | 1.000§ |
| Tenascin superficial† | 14 | 5 | 42 | 17.60/10.980 | 13 | 3 | 22 | 11.73/5.605 | 0.292§ |
| Tenascin deep† | 15 | 8 | 26 | 17.18/6.631 | 1 | 0 | 15 | 2.82/4.600 | **0.000**‡,§ |
| Fibronectin superficial† | 44 | 12 | 59 | 43.27/14.416 | 44 | 25 | 70 | 46.64/14.116 | 0.586// ¶ |
| Fibronectin deep† | 43 | 30 | 61 | 44.00/11.045 | 34 | 12 | 52 | 35.73/10.946 | 0.093// ¶ |

SD: Standard deviation. *results expressed as the number of positive cells per high-power field; †results expressed as the percentage of positive area; ‡statistically significant; §Mann-Whitney U test; //Independent t-test.

superficial (p=0.009) and deep regions (p=0.027), as well as higher tenascin expression in deep regions (p=0.000).

The positivity for p53 was more evident in the superficial fields than in the deep regions of both lesions. p53 expression was absent in one case of GCF, at the deep region, whereas no p53 expression was seen in the superficial region of one TF case and in the deep region of two TF cases. There was no ki-67 expression in superficial regions of three GCF and in deep regions of five GCF. For TF, no expression of ki-67 was observed in the superficial region of six cases and in deep regions of six cases.

All cases of GCF and TF showed positivity for tenascin and fibronectin. In TF, tenascin showed a lower expression in deep regions than in superficial regions. Tenascin showed a vascular-associated pattern in the deep fields of all GCF cases. Fibronectin expression was similar in superficial or deep fields in both lesions.

## DISCUSSION

GCF has low incidence, prevalence, and indolent behavior[2,14]. Thereby, GCF has not been commonly studied, with a few immunohistochemical studies focused on exploring the origin of the giant cells. In an attempt to help understanding if GCF has reactional or neoplastic pathogenesis, this study evaluated the expression of proteins related to tumor suppression, cellular proliferation, and matrix components, compared to the well-known reactive lesion TF. GCF demonstrated higher expression of p53 in superficial and deep regions compared to TF, as well as higher tenascin in deep areas. Ki-67 and fibronectin immunoexpression did not differ between GCF and TF.

The TP53 is a tumor suppressor gene involved in cell cycle regulation, DNA repair, and apoptosis induction. The wild-type p53 protein has a short life and is not detected by immunohistochemistry[8]. Therefore, immunohistochemical analysis detects an altered p53 protein, which is more stable and associated with the loss of tumor suppression functions[8,15]. Previous studies revealed p53 immunoreactivity in benign lesions; despite in smaller proportions when compared to malignant neoplasms[16]. In the present study, GCF had more p53-positive cells in superficial and deep fields than TF. This finding seems to support a neoplastic nature of GCF, which may influence its clinical diagnosis and classification, though further studies shall identify the molecular background of this protein expression. The p53 upper expression was not accompanied by an increased ki-67 expression in GCF, different from what has been shown in other neoplastic lesions[16].

Ki-67 is a nuclear protein expressed during the cell cycle, which is downregulated in G0[9]. Therefore, it is commonly used to identify proliferative human cells[16]. Malignant neoplasms are expected to show high ki-67 indexes, while benign tumors usually have a low proliferation index (<3%)[17]. The low ki-67 index may indicate limited proliferation in GCF, but additional markers are needed to fully understand its biological behavior. Some reactive lesions and benign neoplasms may show ki-67 expression >10%, as shown for nodular fasciitis and myofibromas[18]. Reactive lesions may exhibit increased proliferative activity, mainly during their active growing phase. Souza et al. found higher ki-67 expression in central giant cell granuloma (reactive lesion) compared to giant cell tumor (benign neoplasm)[19]. Moreover, some malignant tumors may exhibit low ki-67 indexes, like acinic cell carcinomas (mean 5.15%), mucoepidermoid carcinomas (mean 5.21%), and polymorphous adenocarcinomas (mean 2.55%)[9]. In the present study, GCF had very low ki-67 indexes, similar to those of TF.

In the present study, we identified the tenascin-C, the most studied member of the tenascin's family (composed by tenascin C, X, R, and W)[12]. Tenascin-C is highly expressed in developing organs, probably by an epithelial-mesenchymal role, standing near motile cells, and decreases during life[11,12,20,21]. In buccal, palatal, tongue, floor of the mouth, and gingival developed mucosa, tenascin is observed as a discontinuous thin layer next to the basement membrane[11,12,20]. Accordingly, all cases in the current study expressed tenascin in the juxtaepithelial region, with no difference between GCF and TF.

Under reactive conditions, wound healing, and tumorigenesis, tenascin expression increases, mainly in areas with inflammatory cells[20]. Accordingly, inflammation is one of the major stimuli for tenascin secretion[11,20]. In wounds, tenascin is expressed following the basement membrane of damaged epithelium, while in solid cancers tenascin is highly expressed in the stroma[11,12,20]. Most studies regarding tenascin expression on neoplastic tissues focus on carcinomas, while studies on benign mesenchymal neoplasms are rare[22]. Schnyder et al. observed a vascular-associated pattern for tenascin in schwannoma and leiomyoma[23], while no expression was detected on lipomas from different sites, including head and neck[22]. On carcinomas and gliomas, the vascular-associated pattern is also present, which may be associated with neovascularization by binding to endothelial cells and promoting its migration and

proliferation[11,24]. The higher expression of tenascin in deep regions of GCF, following a vascular-associated pattern, seems to be an altered expression of this protein, maybe related to a neoplastic nature of GCF.

Fibronectin is a structural glycoprotein expressed by fibroblasts of the extracellular matrix, physiologically acting on cell adhesion to collagen[12]. As fibronectin is a marker of mesenchymal phenotype, it is upregulated in epithelial neoplastic cells during epithelial–mesenchymal transition[25]. Previous studies associated fibronectin up-regulation with invasiveness, metastasis, and an aggressive phenotype in breast cancer, renal cell carcinoma, and ovarian carcinoma[15,25,26]. In benign tumors not located in the mouth, fibronectin was observed to be abundantly expressed in leiomyomas, neurofibroma, and schwannoma[27], but its role is not well described. This study shows that the GCF and TF are immunopositive for fibronectin without statistically significant differences between lesions. This lack of difference can favor a reactive profile for GCF. However, studies comparing reactional and benign tumors are scarce, hampering further comparisons.

The presence of the stellate giant cells in other trauma-induced fibrous lesions of the skin and mucous membranes, like benign polyps, and retrocuspid papillae, could support a reactive nature of GCF[5,14]. On the other hand, studies evaluating collagen fibers from fibrous lesions revealed that the unique GCF fibroblasts have an independent metabolism and are functional in collagen renewal, favoring a neoplastic nature of GCF[28-30]. Moreover, positive staining for the enzyme prolyl-4-hydroxylase was reported in GCF, indicating an active functional phenotype of GCF fibroblasts for collagen synthesis, further corroborating a neoplastic nature of this lesion[4].

Limitations of the study are the small sample size and few markers used. Therefore, generalizability should be done with caution. Future studies on this topic shall overcome the sample size limitation, by using multicenter data. Finally, other markers such as apoptotic proteins and molecular studies on TP53 gene could be evaluated in future research.

## CONCLUSION

In conclusion, the results of the present study are supportive of a benign neoplastic nature of GCF, rather than a reactive one, especially considering the p53 and tenascin expression. From the clinical point of view, this should implicate an autonomous but limited growth capacity of GCF. As a benign tumor, GCF should be treated by conservative surgical excision and recurrences should not be expected. However, additional studies, particularly those involving larger sample sizes and a broader range of markers, are needed to definitively determine the nature of GCF.

## AUTHOR'S CONTRIBUTIONS

IGO: conceptualization, data curation, formal analysis, investigation, writing – original draft. AASC: conceptualization, data curation, formal analysis, investigation, validation, visualization, writing – original draft. DPM: data curation, formal analysis, investigation, writing – original draft. TST: data curation, investigation, writing – review & editing. JJVP: data curation, formal analysis, methodology, software. RAM: formal analysis, investigation, methodology, writing – review & editing. MCRH: conceptualization, writing – review & editing. PCC: conceptualization, funding acquisition, methodology, project administration, resources, supervision, writing – original draft.

## CONFLICT OF INTEREST STATEMENT

**Funding:** Ingrid Gomes de Oliveira was granted a fellowship provided by Pró-Reitoria de Pesquisa da Universidade Federal de Minas Gerais, Conselho Nacional de Desenvolvimento Científico e Tecnológico (PRPq UFMG/CNPq) – Brazil. Grant number: 05/2021.
Adriana Aparecida Silva da Costa and Thalita Soares Tavares were granted a fellowship provided by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) – Brazil. Grant number: Financial code 001.
Daniela Pereira Meirelles was granted a fellowship provided by Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) – Brazil. Grant number: PAPG-13581.
**Competing interests:** The authors have no relevant financial or non-financial interests to disclose.
**Ethics approval:** The study was approved by the Research Ethics Committee of Universidadeßederal de Minas Gerais (certificate number: 15899419.1.0000.5149).

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