Histochemical and immunohistochemical differences between solitary oral fibroma and fibrous papule of the face*

Águida Cristina Gomes Henriques[1]
Bruno Cunha Pires[3]
Jean Nunes dos Santos[1]
Roseana de Almeida Freitas[2]
Clarissa Araújo Gurgel[1]

DOI: http://dx.doi.org/10.1590/abd1806-4841.20165077

Abstract: Background: The morphological similarities between fibrous papules of the face and multiple sporadic oral fibromas were mentioned long ago and a relationship between them has been reported in the literature.
Objective: The aim of this study was to evaluate the participation of mast cells, elastin and collagen in a series of oral fibromas and fibrous papules of the face in order to better understand the possible role of these factors in fibrosis and the formation of these lesions.
Methods: Thirty cases of oral fibroma involving the buccal mucosa and 30 cases of fibrous papules of the face were selected. Tissue samples were submitted to picrosirius red staining and immunohistochemistry using anti-elastin and anti-tryptase antibodies.
Results: The percentage of tryptase-positive mast cells and expression of elastin were higher in cases of fibrous papules of the face ($p < 0.05$). In contrast, a higher intensity of collagen deposition was observed in oral fibromas. The results showed mast cell accumulation and higher elastin synthesis in fibrous papules of the face, and mast cell accumulation with higher collagen fiber synthesis in oral fibromas.
Conclusion: These findings support the hypothesis that mast cells influence the development and growth of these lesions through different mechanisms.
Keywords: Collagen; Elastin; Immunohistochemistry; Mast cells

INTRODUCTION

Fibrous papules (FP) of the face are small, benign swellings on the skin characterized by an increase in blood vessels in the dermis and underlying fibrous stromal tissue. Some authors regard FP as regressed melanocytic nevi, whereas others have suggested these lesions are fibromas with a melanocytic component, or a type of angiofibroma.[1-4] Oral fibroma (OF) is the most common benign tumor of the oral cavity and it is typically characterized by dense, fibrous tissue with numerous fibroblasts and an overlying epithelium that is usually thinned. The term "irritation fibroma" is also used as a synonym for solitary OF, in contrast to OF associated with a phakomatoses, which is usually multiple. [5] The morphological similarities between FP of the face and multiple OF were mentioned long ago, especially when OF appeared in a context of phakomatoses. [4]

A recent study has demonstrated that solitary OF shares many morphological features with FP of the face, including a fibrous and collagenized stroma, dilated blood vessels, concentric perivascular fibrosis and multinucleated cells.[6] This seems to support the hypothesis that sporadic OF is a member of the group of angiofibromatous lesions, which includes FP of the face and multiple fibromas, seen in some phakomatoses.[4]

Much attention has been paid to the participation of mast cells (MC) in the events of extracellular matrix synthesis and remodeling. Mast cells are bone marrow-derived cells, widely found in human tissues.[7,8] The role of MC in connective tissue is still a matter of speculation and it has been suggested that these cells participate in cell regulation and in controlling the accumulation of connective tissue components. Previous reports indicate that MC are poten-

Received on 25.08.2015.
Approved by the Advisory Board and accepted for publication on 09.11.2015.
* Work performed at the Universidade Federal da Bahia (UFBA) – Salvador (BA), Brazil.
Financial Support: None.
Conflict of Interest: None.

[1] Universidade Federal da Bahia (UFBA) – Salvador (BA), Brazil.
[2] Universidade Federal do Rio Grande do Norte (UFRN) – Natal (RN), Brazil.
[3] Private clinic – Feira de Santana (BA), Brazil.

tially fibrogenic since they secrete potent mediators of fibrosis.[9,10] The identification of MC subpopulations requires the detection of enzymes secreted by these cells, mainly tryptase and chymase.[11,12] Tryptase is found in all human MC, but has not been detected in any other cell type. Therefore, the detection of tryptase in human biological fluids and tissues is interpreted as an indicator of mast cell activation.[13]

The secretion of endopeptidases by MC modulates inflammation, matrix destruction, tissue remodeling, and angiogenesis.[14-17] Studies have shown that tryptase upregulates fibroblast proliferation, indicating that, once activated, MC can affect the mitogen-induced proliferation of fibroblasts and stimulate fibrosis.[18,19] Direct and/or indirect interactions between MC and fibroblasts promote connective tissue reorganization. The process of tissue remodeling involves the synthesis of all extracellular matrix components by fibroblasts, including collagen and elastin fibers. Elastin and microfibrils comprise the elastic fiber system. Studies have demonstrated the participation of elastin in the development of fibrous lesions in the oral mucosa.[20] In this respect, fibroblasts that are stimulated by chemical mediators released by MC are expected to produce higher amounts of the fibrillar component of extracellular matrix, thus contributing to tissue fibrogenesis.

The aim of this study was to evaluate the participation of mast cells, elastin and collagen in a series of sporadic OF and FP of the face using immunohistochemical and histochemical methods, in order to better understand the possible role of these factors in fibrosis and the formation of these lesions.

METHODS

The sample consisted of 60 paraffin-embedded tissue specimens, including 30 cases of solitary OF of the buccal mucosa and 30 FP of the face, obtained from the Pathological Anatomy Service of the Department of Oral Pathology and from a private surgical pathology laboratory, respectively. None of the patients had phakomatosis.

Histochemistry

To evaluate the intensity of collagen deposition, 5-µm-thick sections were stained with picrosirius red and analyzed under an Olympus CX31 light microscope. The following scores were attributed: (weak) ≤ 50% stained fibers, and (strong) > 50% stained fibers.

Immunohistochemical analysis

For the immunohistochemistry, 3-µm-thick sections were cut from paraffin-embedded tissue blocks, deparaffinized, and immersed in 3% hydrogen peroxide to block endogenous peroxidase activity. The sections were then washed in phosphate-buffered saline (PBS) and submitted to antigen retrieval (Table 1). After treatment with normal serum, the sections were incubated with the primary anti-tryptase and anti-elastin antibodies in a moist chamber (Table 1). Next, the sections were washed twice in PBS and incubated at room temperature with the labeled streptavidin biotin complex (LSAB+ System-HRP, Dako, Carpinteria, CA, USA) for anti-elastin and anti-tryptase antibodies. Peroxidase activity was visualized by immersing the tissue sections in diaminobenzidine (Liquid DAB+ Substrate, Dako), which resulted in a brown reaction product. Finally, the sections were counterstained with Mayer's hematoxylin and coverslipped. Sections of pyogenic granuloma and actinic cheilitis were used as positive controls for MC tryptase and elastin, respectively. As a negative control, the sections were treated as described above, except that the primary antibody was replaced with a solution of bovine serum albumin in PBS.

The slides were examined under an Olympus CX31 light microscope. Immunoreactivity of MC to the anti-tryptase antibody was analyzed quantitatively in the lining epithelium and in connective tissue of the specimens. Areas of high MC density were identified at 100x magnification. The number of tryptase-positive MC was determined in up to 10 high-power fields at 400x magnification, using a digital camera for recording. Mast cells were counted using the Image J program and the mean number of positive cells was calculated for each case. The expression of elastin was analyzed in up to 10 fields at 100x magnification, applying scores ranging from +3 to 0, adapted from Fukushima *et al.* and Araújo *et al.* [21,22] A score of +3 corresponds to a diffuse increase of elastic fibers with mass pattern; +2 signifies a diffuse increase of elastic fibers; +1 reflects partial increase with focal clusters of elastic fibers; while 0 denotes the same characteristics as observed in the control group. The thickness and fragmentation of elastic fibers were also described.

Differences between groups were evaluated by the Chi-square test, Student *t*-test and Mann-Whitney test. All statistical calculations were performed using the Statistical Package for the Social Sciences 17.0 (SPSS, Inc., Chicago, IL, USA). A p value < 0.05 was deemed statistically significant.

RESULTS

A fibrotic and collagenized hypocellular stroma with a sparse inflammatory cell infiltrate was observed in all lesions. Multinucleated cells were scattered and non-abundant in FP. The number of dilated vessels ranged from minimal in OF to substantial in FP. Concentric fibrosis around the vessels was not a prominent feature. Hair follicles, sebaceous glands and periadnexal dermis were were seen in FP, but not in OF. Vascular ectasia and perivascular fibrosis were also less striking in OF.

Table 1: Specifications of the antibodies used

Antibody	Manufacturer	Clone	Antigen retrieval	Dilution	Incubation
Tryptase	Abcam	AA1	Citrate, pH 6.0, Pascal	1:200	30′
Elastin	Novocastra	BA4	0.1% trypsin, 30′, 37°C	1:50	60′

Comparison of the intensity of collagen deposition between the two groups of lesions showed strong picrosirius red staining in all OF cases, whereas weak staining was observed in most FP cases ($p < 0.001$, X^2) (Figure 1).

Mast cells were detected in all OF and FP cases. The mean total number of tryptase-positive MC was 167.4 (SD: 51.171) in FP and 64.63 (SD: 17.022) in OF (Figure 2). The parametric *t*-test revealed a statistically significant difference between groups ($p < 0.001$). Tryptase-positive MC were detected only in connective tissue, mainly at the periphery of blood vessels (perivascular MC). The presence of MC in FP or OF was not associated with an inflammatory response since the infiltrate of inflammatory cells was sparse.

Analysis of the expression of elastin in FP showed a score of +3 in four cases, +2 in twelve, +1 in five, and 0 in nine (Figure 3). For OF, twenty-four cases were scored as zero; only six had a score of +1, while there were no scores of +2 or +3 (Figure 3). Scores +2 and +3 were more frequent in FP. The nonparametric Mann-Whitney test revealed a statistically significant difference between groups ($p < 0.001$). The elastic fibers exhibited variable degrees of thickness, but were thin and fragmented in most cases. Elastic fibers were also present in the submucosa, though in lower quantities.

DISCUSSION

The results reflected differences in the number of MC, collagen and elastin between FP and OF, indicating that these components seem to influence the development of these lesions.

Mast cells are found in almost all organs and tissues of the human body and are the main source of histamines, proteases, and other important chemical mediators. The major component present in the secretory granules of MC is tryptase, an enzyme released along with other mediators in the extracellular matrix after the activation/degranulation of MC.[23,24] It has been suggested that tryptase stimulates the proliferation of fibroblasts and synthesis of collagen, and that it is involved in fibrinogenesis.[23,25] In addition, tryptase plays a role in other biological activities, such as: the stimulation of the proliferation of smooth muscle cells and bronchial epithelial cells, the degradation of vasoactive intestinal peptide, and angiogenesis. [26-28] In the oral mucosa, MC are involved in the induction of fibrosis and modulation of endothelial cell function in inflammatory fibrous hyperplasia and giant cell fibroma.[23] Furthermore, there is evidence of a parallel increase in tryptase-positive MC and angiogenesis in normal oral mucosa, epithelial dysplasia and squamous cell carcinoma.[29]

In this study, the number of tryptase-positive MC was higher in FP of the face than in solitary OF. The presence of MC in FP and OF suggests aberrant extracellular matrix remodeling during the growth of these lesions. One possible explanation for the larger number of MC in FP is the marked vascularization observed in these lesions, which correspond to a type of angiofibroma. Another plausible explanation is that FP can be triggered by exposure to ultraviolet radiation, which seems to affect directly MC, altering their potential to release mediators.[30,31] Some investigators have shown

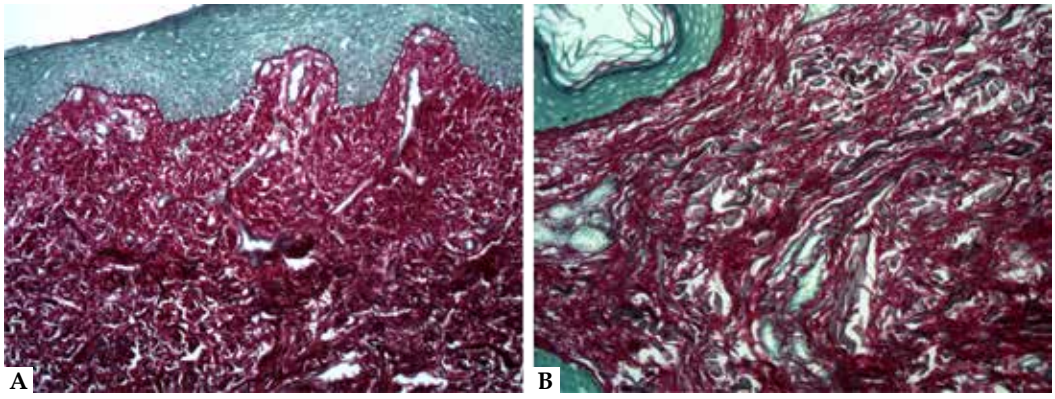

Figure 1: Picrosirius red. Histologic sections showing strong picrosirius red staining in OFs (A), compared with FP with less intensely staining (B) (200X)

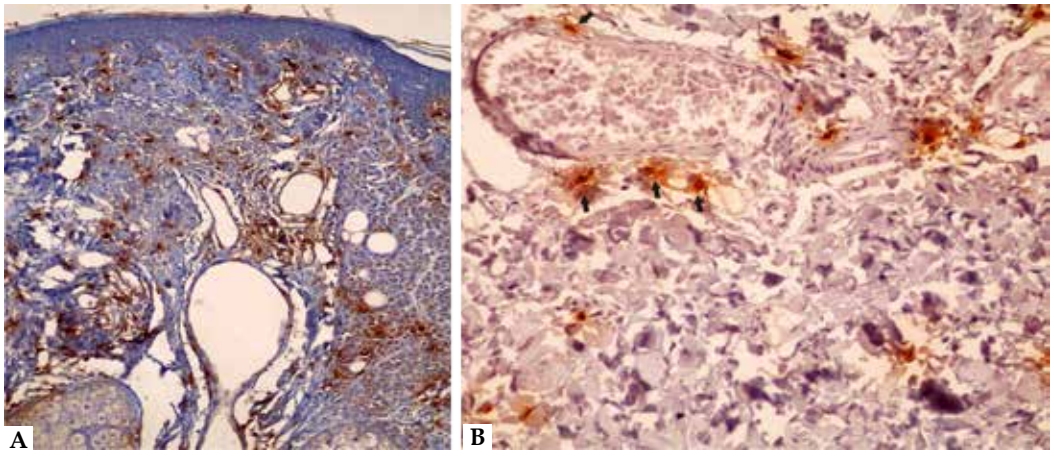

Figure 2: Tryptase. Note the tryptase-positive MCs in FP (A) and in OF (B) (400x). Tryptase-positive MCs (arrow) at the periphery of blood vessels (B) (400X)

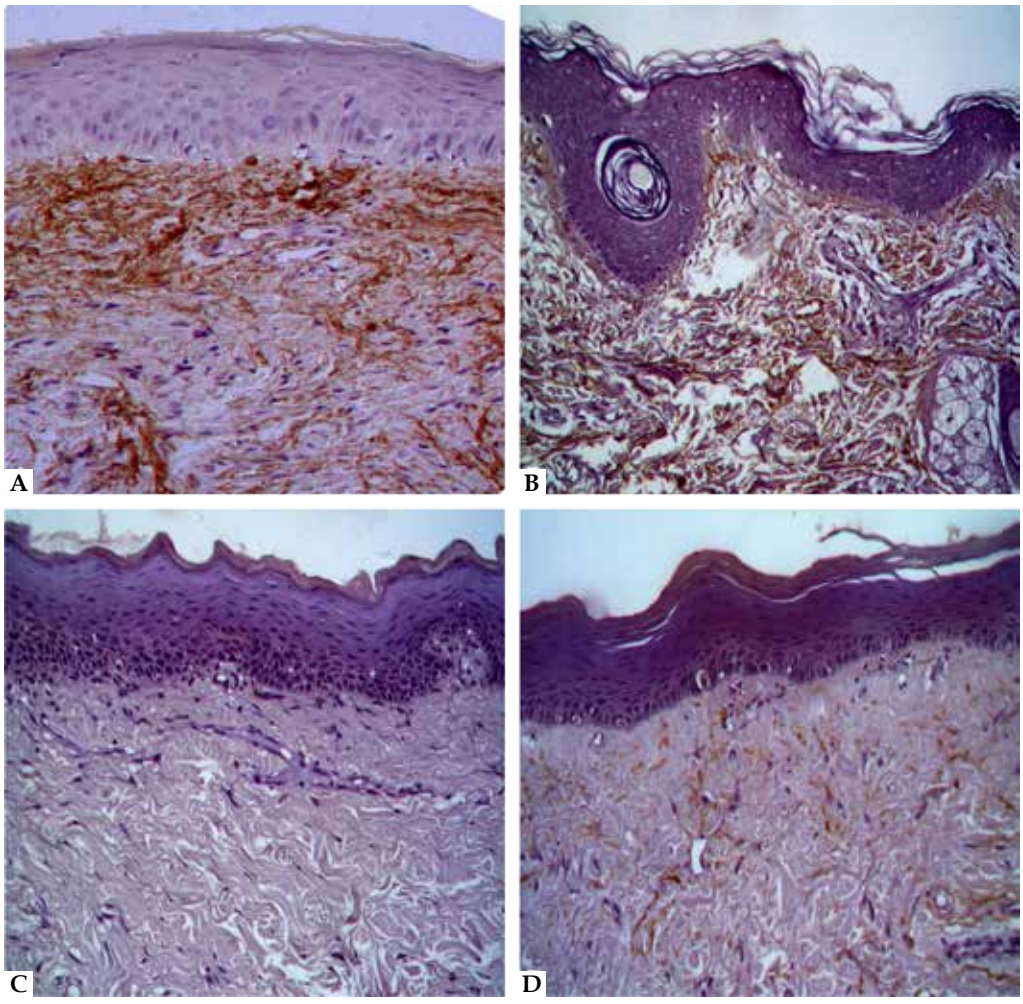

Figure 3:
Elastin. Histologic sections showing expression of elastin with score of +3 (A) (200x) and +2 (B) (200x) in FPs. Note in C and D (200x), expression of elastin with score of 0 and +1 in OFs, respectively

that the number of MC increases significantly in skin exposed to sunlight.[32,33]

In the lesions studied (FP and OF), most tryptase-positive MC were detected in connective tissue, mainly at the periphery of blood vessels. Nevertheless, there appears to be intimate cellular communication between this cell population and the vascular system. Mast cells produce and release proteolytic enzymes, tryptase and chymase, which mediate the migration of endothelial cells and the release of angiogenic factors, such as vascular endothelial growth factor (VEGF), basic fibroblastic growth factor (b-FGF), transforming growth factor-beta (TGF-b), tumor necrosis factor-alpha (TNF-α), and interleukin (IL)-8, creating a microenvironment that favors neoplastic development. [24,34]

The large mean number of MC in FP suggests that these cells may be responsible for the stimulation of fibroblast proliferation and fibrous stroma formation in lesions. However, high concentrations of MC in areas of fibrosis have been observed in different types of lesions. Vidal *et al.* detected high concentrations of MC in many cases of pleomorphic adenoma and in the fibrous matrix of malignant, minor, salivary gland tumors.[17] Ahmed *et al.* suggested a direct relationship between MC and intramedullary fibrosis. Pereira *et al.* raised the hypothesis of the growth and expansion of odontogenic tumors through collagen synthesis mediated by MC.[34,35] The results reported by Epivatianos *et al.* indicate that tryptase-containing MC are involved in the fibrosis of chronic submandibular sialadenitis.[36] During breast cancer progression, MC have been shown to contribute to tissue remodeling, characterized by the differentiation of fibroblasts into myofibroblasts, through the release of tryptase into the tumor stroma.[16]

Fibroblast proliferation is a characteristic event of connective tissue reorganization, wound healing, and fibrosis. This was demonstrated by Riekki *et al.*, who investigated the role of MC in tissues submitted to radiotherapy and advocated that these cells are involved in enhanced skin collagen synthesis and the induction of fibrosis during the reorganization of damaged connective tissue.[37] Studies have suggested MC play an important role in fibroproliferative diseases, particularly as a result of the secretion of different chemical mediators, including tryptase. [38] Secreted by MC, tryptase interacts with protease activation receptor (PAR-2), inducing the proliferation of fibroblasts. [18,19] Coussens *et al.* demonstrated the role of chymase and tryptase secreted by MC in tissue remodeling.[39] Tryptase was found to stimulate dermal fibroblasts, inducing DNA synthesis in quiescent cells, and to increase α-1 collagen production in MC-rich areas *in vivo*.

We observed no association between the number of MC and the presence of a significant inflammatory process. These results agree with the findings of Smith *et al.* and Pereira *et al.*, who also found no relationship between the presence of these cells and inflammation in other lesions.[34, 40]

Interestingly, in this study, the expression of collagen fibers was higher in OF than in FP, as would be expected, since the latter exhibited a larger number of MC. On the other hand, we observed a higher expression of elastin in FP than in OF. The high expression of elastin in FP may be related to the high concentration of MC, as fibroblasts also synthesize elastic fibers. It is therefore possible that MC also influence the deposition of elastin by stimulating fibroblasts through the secretion of chemical mediators. In addition, we believe that ultraviolet radiation has a significant effect on tissue remodeling and fibrosis in FP, based on the hypothesis that fibrocytes altered by ultraviolet radiation are related to induce the synthesis and excessive deposition of elastic material.[22,41,42] Hence, fibroblasts involved in tissue remodeling in FP differ phenotypically from those involved in the development of OF, suggesting differences in matrix composition between these lesions. The stronger association between MC accumulation and elastin synthesis in FP -in contrast to OF in which MC accumulation was associated with the synthesis of collagen fibers- supports the hypothesis that MC influence the growth and expansion of OF and FP through different mechanisms.

A relationship between FP and OF has been reported in the literature. According to Fernandez-Flores, these lesions seem to be part of the same group of angiofibromatous lesions, since they share some microscopic features. [6] However, the morphological findings of this study indicate that blood vessels, multinucleated cells, vascular ectasia and perivascular fibrosis are less frequent in OF, as also reported by Reed and Ackerman.[4] Moreover, hair follicles, sebaceous glands, and periadnexal dermis are absent in OF. The differences in the expression of collagen, elastin and MC observed in this study between FP and OF suggest these lesions have a distinct etiopathogenesis. This does not seem to support the hypothesis that sporadic OF is a member of the group of angiofibromatous lesions, which includes FP of the face and multiple fibromas, seen in some phakomatoses.[6] The results suggest that a greater involvement of MC in the formation of fibrous tissue in FP, and that ultraviolet radiation influences both the concentration of MC and the synthesis of the fibrillar component found in the fibrous matrix of these lesions.

CONCLUSION

MC tryptase activates fibroblasts to produce collagen and elastin, thus contributing to fibrosis in FP and OF. The results suggest that the MC population and the intensity of collagen and elastin expression can contribute for the morphological differences between FP and OF.❑

REFERENCES

1. Saylan T, Marks R, Jones EW. Fibrous papule of the nose. Br J Dermatol. 1971;85:111-8.
2. McGibbon DH, Jones EW. Fibrous papule of the face (nose). Fibrosing nevocytic nevus. Am J Dermatopathol. 1979;1:345-8.
3. Reed RJ, Hairston MA, Palomeque FE. The histologic identity of adenoma sebaceum and solitary melanocytic angiofibroma. Dermatol Int. 1966;5:3-11.
4. Reed RJ, Ackerman AB. Pathology of the adventitial dermis. Anatomic observations and biologic speculations. Hum Pathol. 1973;4:207-17.
5. Sparling JD, Hong CH, Brahim JS, Moss J, Darling TN. Oral findings in 58 adults with tuberous sclerosis complex. J Am Acad Dermatol. 2007;56:786-90.
6. Fernandez-Flores A. Solitary oral fibromas of the tongue show similar morphologic features to fibrous papule of the face: a study of 31 Cases. Am J Dermatopathol. 2010;32:442-7.
7. Rodewald HR, Dessing M, Dvorak AM, Galli SJ. Identification of a committed precursor for the mast cell lineage. Science. 1996;271:818-22.
8. Chen CC, Grimbaldeston MA, Tsai M, Weissman IL, Galli SJ.. Identification of mast cell progenitors in adult mice. Proc Natl Acad Sci U S A. 2005;102:11408-13.
9. Berton A, Levi-Schaffer F, Emonard H, Garbuzenko E, Gillery P, Maquart FX.. Activation of fibroblasts in collagen lattices by mast cell extract: a model of fibrosis. Clin Exp Allergy. 2000;30:485-92.
10. Garbuzenko E1, Nagler A, Pickholtz D, Gillery P, Reich R, Maquart FX, et al. Human mast cells stimulate fibroblast proliferation, collagen synthesis and lattice contraction: a direct role for mast cells in skin fibrosis. Clin Exp Allergy. 2002;32:237-46.
11. Rojas IG, Spencer ML, Martínez A, Maurelia MA, Rudolph MI. Characterization of mast cell subpopulations in lip cancer. J Oral Pathol Med. 2005;34:268-73.
12. Caughey GH. Mast cell tryptases and chymases in inflammation and host defense. Immunol Rev. 2007;217:141-54.
13. Harvima RJ, Harvima IT, Dull D, Dunder UK, Schwartz LB. Identification and characterization of multiple forms of tryptase from human mast cells. Arch Dermatol Res. 1999;291:73-80.
14. Norrby K. Mast cells and angiogenesis. APMIS. 2002;110:355-71.
15. Maltby S, Khazaie K, McNagny KM. Mast cells in tumor growth: angiogenesis, tissue remodelling and immune-modulation. Biochim Biophys Acta. 2009;1796:19-26.
16. Mangia A, Malfettone A, Rossi R, Paradiso A, Ranieri G, Simone G, et al. Tissue remodeling in breast cancer: human mast cell tryptase as an initiator of myofibroblasts differentiation. Histopathology. 2011;58:1096-106.
17. Vidal MT, de Oliveira Araújo IB, Gurgel CA, Pereira Fde A, Vilas-Bôas DS, Ramos EA, et al. Density of mast cells and microvessels in minor salivary gland tumors. Tumour Biol. 2013;34:309-16.
18. Levi-Schaffer F, Piliponsky AM. Tryptase a novel link between allergic inflammation and fibrosis. Trends Immunol. 2003;24:158-61.
19. Matsushima R, Takahashi A, Nakaya Y, Maezawa H, Miki M, Nakamura Y, et al. Human airway trypsin-like protease stimulates human bronchial fibroblast proliferation in a protease-activated receptor-2-dependent pathway. Am J Physiol Lung Cell Mol Physiol. 2006;290:L385-95.
20. Mighell AJ, Robinson PA, Hume WJ. Histochemical and immunohistochemical localization of elastic system fibres in focal reactive overgrowths of oral mucosa. J Oral Pathol Med. 1997;26:153-8.
21. Fukushima H, Ohsawa M, Ikura Y, Naruko T, Sugama Y, Suekane T, et al. Mast cells in diffuse large B-cell lymphoma; their role in fibrosis. Histopathology. 2006;49:498-505.
22. Araújo CP., Xavier FCA., Gurgel CAS, et al. Elastin accumulation in actinic cheilitis with different degrees of epithelial dysplasia. Int J Morphol. 2012;30:627-33.
23. Santos PP, Nonaka CF, Pinto LP, de Souza LB. Immunohistochemical expression of mast cell tryptase in giant cell fibroma and inflammatory fibrous hyperplasia of the oral mucosa. Arch Oral Biol. 2011;56:231-7.
24. Lima SC, Rizo VH, Silva-Sousa YT, Almeida LY, Almeida OP, León JE. Immunohistochemical evaluation of angiogenesis and tryptase-positive mast cell infiltration in periapical lesions. J Endod. 2011;37:1642-6.
25. Huttunen M, Harvima IT. Mast cell tryptase and chymase in chronic leg ulcers: chymase is potentially destructive to epithelium and is controlled by proteinase inhibitors. Br J Dermatol. 2005;152:1149-60.
26. Kondo S1, Kagami S, Kido H, Strutz F, Müller GA, Kuroda Y. Role of mast cell tryptase in renal interstitial fibrosis. J Am Soc Nephrol. 2001;12:1668-76.
27. Shimizu Y, Suga T, Maeno T, Tsukagoshi H, Kawata T, Narita T, et al. Detection of tryptase, chymase cells in human CD34 bone marrow progenitors. Clin Exp Allergy. 2004;34:1719-24.
28. Caughey GH. Mast cell tryptases and chymases in inflammation and host defense. Immunol Rev. 2007;217:141-54.
29. Iamaroon A, Pongsiriwet S, Jittidecharaks S, Pattanaporn K, Prapayasatok S, Wanachantararak S. Increase of mast cells and tumor angiogenesis in oral squamous cell carcinoma. J Oral Pathol Med. 2003;32:195-9.
30. Guhl S, Stefaniak R, Strathmann M, Babina M, Piazena H, Henz BM, et al. Bivalent effect of UV light on human skin mast cells-low-level mediator release at baseline but potent suppression upon mast cell triggering. J Invest Dermatol. 2005;124:453-6.
31. Araújo CP, Gurgel CA, Ramos EA, Freitas VS, Barbosa Ade A Jr, Ramalho LM, et al. Accumulation of CD1a-positive Langerhans cells and mast cells in actinic cheilitis. J Mol Histol. 2010;41:357-65.
32. Grimbaldeston MA, Finlay-Jones JJ, Hart PH. Mast cells in photodamaged skin: what is their role in skin cancer? Photochem Photobiol Sci. 2006;5:177-83.
33. Gomes AP, Johann JE, Lovato GG, Ferreira AM. Comparative analysis of the mast cell density in normal oral mucosa, actinic cheilitis and lip squamous cell carcinoma. Braz Dent J. 2008;19:186-9.
34. de Assis Caldas Pereira F, Gurgel CA, Ramos EA, Vidal MT, Pinheiro AL, Jurisic V, et al. Distribution of mast cells in benign odontogenic tumors. Tumour Biol. 2012;33:455-61.
35. Ahmed A, Powers MP, Youker KA, Rice L, Ewton A, Dunphy CH, et al. Mast cell burden and reticulin fibrosis in the myeloproliferative neoplasms: a computer-assisted image analysis study. Pathol Res Pract. 2009;205:634-8.
36. Epivatianos A, Zaraboukas T, Poulopoulos A, Harrison JD. Immunohistochemical study of fibroblasts and mast cells in chronic submandibular sialadenitis. Oral Dis. 2008;14:259-63.
37. Riekki R, Harvima IT, Jukkola A, Risteli J, Oikarinen A. The Production of collagen and the activity of mast-cell chymase increase in human skin after irradiation therapy. Exp Dermatol. 2004;13:364-71.
38. Farahani SS, Navabazam A, Ashkevari FS. Comparison of mast cells count in oral reactive lesions. Pathol Res Pract. 2010;206:151-5.
39. Coussens LM, Raymond WW, Bergers G, Laig-Webster M, Behrendtsen O, Werb Z, et al. Inflammatory mast cells up-regulate angiogenesis during squamous epithelial carcinogenesis. Genes Dev. 1999;13:1382-97.
40. Smith G, Smith AJ, Basu MK. Mast cells in human odontogenic cysts. J Oral Pathol Med. 1989;18:274-8.
41. Just M, Ribera M, Monsó E, Lorenzo JC, Ferrándiz C. Effect of smoking on skin elastic fibres: morphometric and immunohistochemical analysis. Br J Dermatol. 2007;156:85-91.
42. Philips N, Keller T, Hendrix C, Hamilton S, Arena R, Tuason M, et al. Regulation of the extracellular matrix remodeling by lutein in dermal fibroblasts, melanoma cells, and ultraviolet radiation exposed fibroblasts. Arch Dermatol Res. 2007;299:373-9.

MAILING ADDRESS:
Águida Cristina Gomes Henriques
Av. Araújo Pinho, 62
Canela
40110-150 Salvador – BA.
Brazil
E-mail: aguidacgh@gmail.com

How to cite this article: Henriques ACG, Freitas RA, Pires BC, Gurgel CA, Santos JN. Histochemical and immunohistochemical differences between solitary oral fibroma and fibrous papule of the face. An Bras Dermatol. 2016;91(5):589-94.