Immunohistochemical expression of matrilysins (MMP-7 and MMP-26) in ameloblastomas and adenomatoid odontogenic tumors

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Objective. The aim was to evaluate the expression of matrix metalloproteinases (MMPs) 7 and 26 in ameloblastomas and adenomatoid odontogenic tumors (AOTs).

Study design. Twenty intraosseous solid ameloblastomas and 10 intraosseous AOTs were evaluated regarding immunohistochemical expression of MMP-7 and -26 in the epithelium and stroma.

Results. There was no statistically significant difference in MMP-7 and -26 expression between the epithelium of ameloblastomas ($P = .50$) and AOTs ($P = .90$). Stromal staining for MMP-7 was evident in all cases. For MMP-26, stromal staining was observed in 65% of ameloblastomas and 50% of AOTs, and this difference was not statistically significant ($P = .69$).

Conclusion. The marked expression of these matrilysins suggests their role in the process of tissue remodeling and growth in the studied tumors, but it does not relate to the their distinct patterns of aggressiveness. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;108:417-424)**

Ameloblastoma is the most frequent tumor of epithelial odontogenic origin.[1] Although benign, it is locally invasive, with a high recurrence rate if not adequately removed. The World Health Organization (WHO) has recently classified it into 4 variants: solid (multicystic ameloblastoma), extraosseous (peripheral ameloblastoma), desmoplastic, and unicystic.[2]

Adenomatoid odontogenic tumor (AOT) is a rather uncommon tumor of odontogenic origin.[3,4] Its clinical and microscopic characteristics, biologic behavior, and prognosis are distinct from ameloblastoma. AOT presents an indolent behavior with rare recurrences, allowing a conservative treatment compared with that recommended for solid ameloblastomas.[2,5]

Matrix metalloproteinases (MMPs) are a family of zinc- and calcium-dependent proteolytic enzymes that degrade the extracellular matrix (ECM) into macromolecules, such as collagen, gelatin, fibronectin, tenascin, and laminin, at physiologic pH.[6] More than 20 different members are currently known and classified according to the domain organization: collagenases (MMP-1, -8, -13, and -18), gelatinases (MMP-2 and -9), stromelysins (MMP-3 and -10), matrilysins (MMP-7, -26, and -11), membrane-type MMPs (MMP-14, -15, -16, -17, -24, and -25), and other MMPs (MMP-12, -19, -20, -21, -23, -27, and -28).[7]

In physiologic conditions, MMPs play a central role in the regulation of the ECM during embryonic development and tissue remodeling.[7,8] However, the degradation of ECM has also been associated with diverse pathologic processes, including tumor growth, invasion, and metastasis.[9,10]

The matrilysins, also known as MMP-7 (matrilysin-1) and MMP-26 (matrilysin-2), are involved in cell proliferation, apoptosis, invasion, and metastasis. These matrilysins differ from other MMPs in their low molecular weight, their lack of a C-terminal hemopexin domain common to other MMPs, and their low expression in epithelial cells in physiologic conditions.[11] Research has demonstrated their expression in malignant epithelial neoplasms[12,13] and odontogenic keratocysts.[14] However, no study has shown their expression in ameloblastoma and AOT.

Table I. Monoclonal antibodies used

Antibody clones	Specificity	Dilution	Antigen retrieval	Incubation
Ab-1/ID2*	MMP-7	1:250	Pepsin pH 1.8, oven 37°C, 60 min	Overnight (18 h)
AHP756†	MMP-26	1:250	Pepsin pH 1.8, oven 37°C, 60 min	Overnight (18 h)

*Labvision/Neomarkers, Fremont, CA.
†Serotec, Kidlington, Oxford, U.K.

In the present study, the expression of MMP-7 and MMP-26 in ameloblastoma and AOT was examined through immunohistochemistry, to clarify the possible role of these matrilysins in the biologic behavior of these tumors.

MATERIALS AND METHODS

Twenty cases of intraosseous solid ameloblastoma (14 of the follicular and 6 of the plexiform pattern) and 10 of intraosseous AOTs were obtained from the files of the Oral Pathology Department of the Federal University of Rio Grande do Norte (UFRN). Diagnoses were confirmed by the authors through the review of hematoxylin and eosin–stained sections, following the WHO classification.[2] The specimens, embedded in paraffin blocks, were sliced in 3-μm-thick tissue sections and submitted to immunohistochemical examination. The study was approved by the Research Ethics Committee at UFRN.

Immunohistochemical methods

The tissue sections were deparaffinized and immersed in methanol with 0.3% hydrogen peroxide to block endogenous peroxidase activity. Tissue sections were then washed in phosphate-buffered saline (PBS). The antigen retrieval, antibody dilution, and clone type for MMP-7 and -26 are shown in Table I. After treatment with normal serum, the sections were incubated in a moist chamber with primary antibodies. The sections were then washed twice in PBS and treated with streptavidin-biotin-peroxidase complex (Dako, Glostrup, Denmark) at room temperature to bind the primary antibodies. Peroxidase activity was visualized by immersing tissue sections in diaminobenzidine (D5637; Sigma Chemical, St. Louis, MO), resulting in a brown reaction product. Finally, tissue sections were counterstained with Mayer hematoxylin and coverslipped. Positive controls for MMP-7 and -26 were sections of ordinary human placenta. As negative controls, samples were treated as above, except that the primary antibody was replaced by a solution of bovine serum albumin in PBS.

Immunohistochemical expression evaluation and statistical analysis

Immunohistochemical staining of MMP-7 and -26 was evaluated using descriptive and semiquantitative

Table II. Immunoreactive scores used for analysis of metalloproteinases in the epithelium

Score	Immunopositive cells
1	<10%
2	10%-50%
3	>50%

analysis. In the latter analysis, scores from 1 to 3 were used for the stained cells in the epithelium (Table II). Staining in the stroma was evaluated and classified as positive (+) and negative (−). Parameters were independently analyzed through light microscopy by 3 of the authors. Then they analyzed the cases as a group to reach a consensus.

Statistical analysis was performed using SPSS for Windows version 15.0 (SPSS, Chicago, IL). The Mann-Whitney test was performed in the epithelium immunoscores, and the chi-squared test in the stroma staining. P values of <.05 were considered to indicate statistical significance.

RESULTS

The majority of both the ameloblastomas (60%) and the AOTs (70%) showed score 3 for MMP-7 in the epithelium. In the ameloblastoma, staining was especially evident in central cells of epithelial nests (Fig. 1, A and B). Stromal staining was observed in all studied cases in fibroblasts and inflammatory and endothelial cells (Fig. 1, E). In AOT, staining for this matrilysin was evident in cuboidal and columnar epithelial cells present in nests and duct-like structures (Fig. 1, C and D). Stromal staining in AOT was shown in some fibroblasts and endothelial cells (Fig. 1, F).

The expression analysis of MMP-26 in the ameloblastoma epithelium showed that 55% of the ameloblastomas exhibited score 3. A variation in the location pattern of the stained cells was observed. In the plexiform pattern, expression was more homogeneously distributed (Fig. 2, A), whereas in the follicular pattern immunoreactivity was especially observed in central cells of nests (Fig. 2, B). In the AOT epithelium, 50% of the cases presented score 3. Staining was shown in nests and duct-like and rosette-like structures (Fig. 2, C and D). In the stroma, it was observed that 65% of the
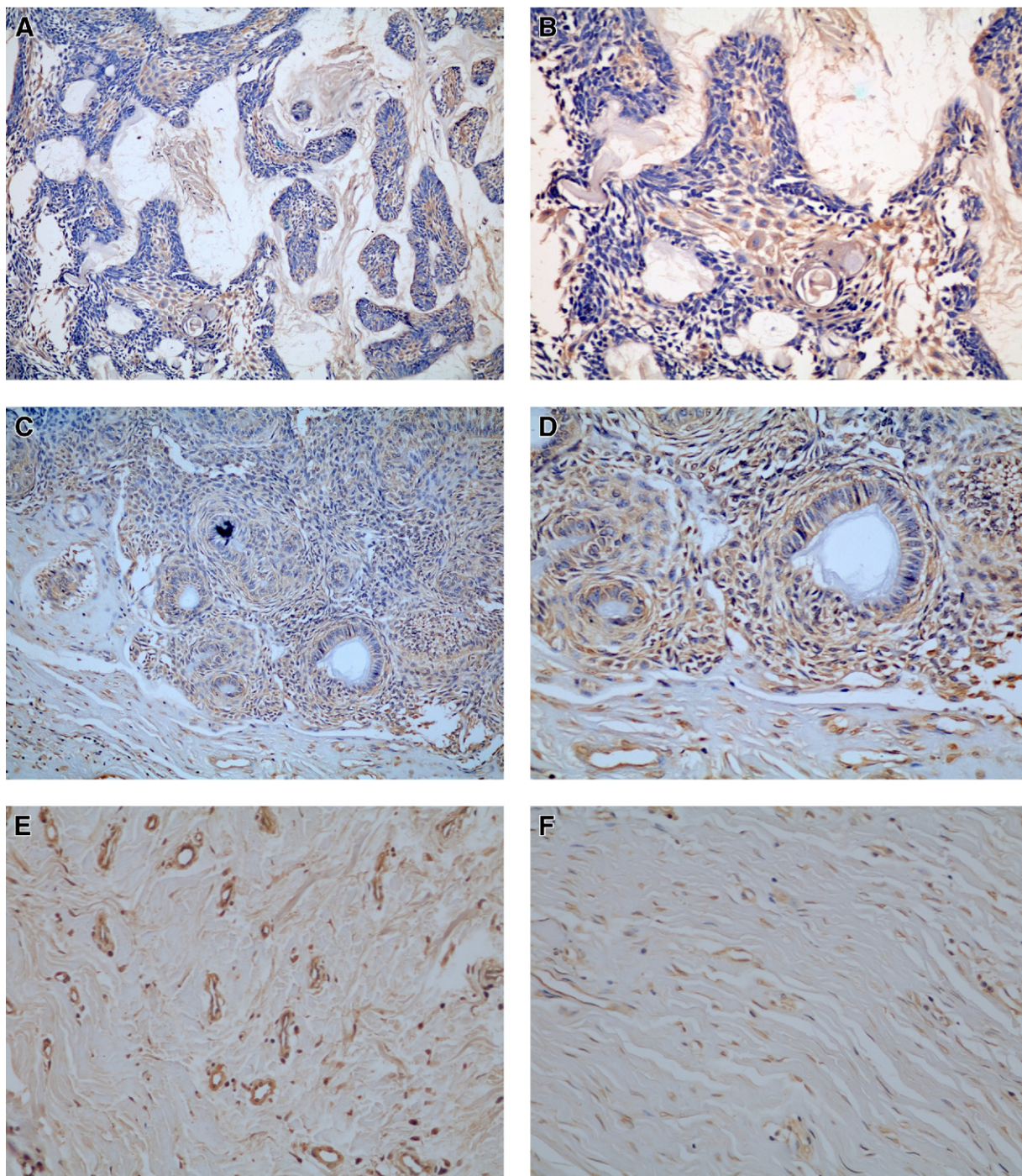
Fig. 1. Immunohistochemical reactivity for matrilysin-1 (metalloproteinase 7) in ameloblastomas and adenomatoid odontogenic tumors (AOTs). **A,** Ameloblastoma showing expression in epithelium (×200). **B,** Ameloblastoma showing expression in central cells of epithelial nests (×400). **C,** AOT showing expression in epithelium (×200). **D,** AOT showing strong expression in epithelial cells in nests and duct-like structures (×400). **E,** Ameloblastoma showing expression in fibroblasts and inflammatory and endothelial cells (×400). **F,** AOT showing expression in fibroblasts and endothelial cells (×400).

ameloblastomas and 50% of the AOTs exhibited staining for MMP-26. Stromal staining for this matrilysin was similar for both tumors, being observed in fibroblasts as well as in endothelial cells (Fig. 2, E and F).

Table III shows that there was no significant difference between the metalloproteinase staining medians in the ameloblastoma epithelium and the AOTs. The same was observed when comparing MMP-7 ($P = .50$) and
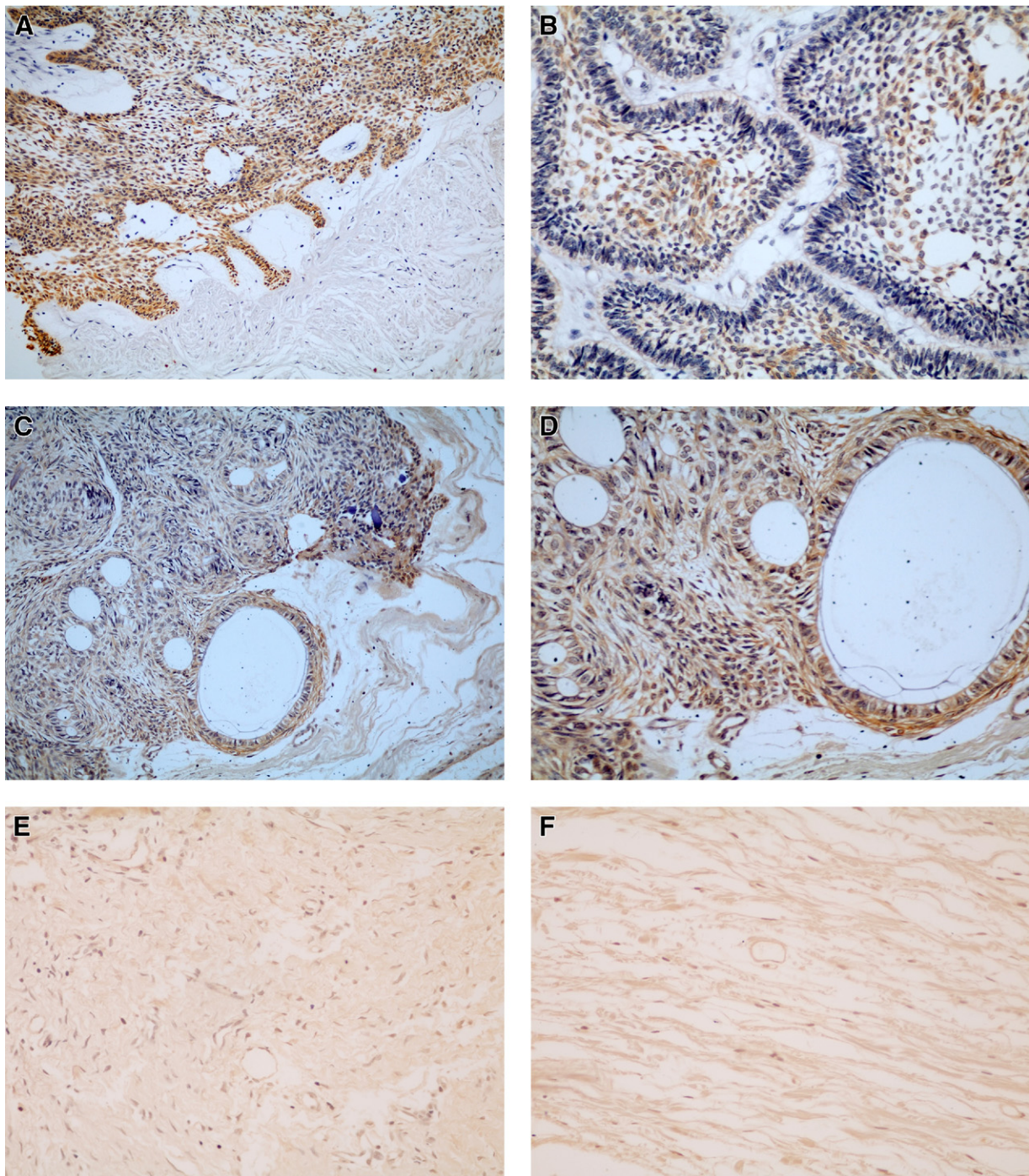
Fig. 2. Immunohistochemical reactivity for matrilysin-2 (metalloproteinase 26) in ameloblastomas and adenomatoid odontogenic tumors (AOTs). **A,** Plexiform ameloblastoma showing expression in epithelium (×200). **B,** Follicular ameloblastoma showing expression in central cells of epithelial nests (×400). **C,** AOT showing expression in epithelium (×200). **D,** AOT showing expression in epithelial cells in nests and duct-like and rosette-like structures (×400). **E,** Ameloblastoma showing expression in fibroblasts and endothelial cells (×400). **F,** AOT showing expression in fibroblasts and endothelial cells (×400).

MMP-26 ($P = .90$) staining between the 2 lesions. The chi-squared test (Table IV) also showed no significant difference in stromal MMP-26 staining between the 2 lesions. Regarding MMP-7, no statistical tests were performed, because its presence was verified in 100% of the samples of both lesions.

Table III. Immunoscores of the metalloproteinases (MMPs) in tumoral epithelium, expressed with medians, quartiles, and rank means

MMP	Lesion	n	Median	Q25	Q75	Rank mean	P value
MMP-7	Ameloblastoma	20	3.00	2.00	3.00	14.85	.50
	AOT	10	3.00	2.00	3.00	16.80	
MMP-26	Ameloblastoma	20	3.00	2.00	3.00	15.38	.90
	AOT	10	2.50	2.00	3.00	15.75	

Table IV. Immunoreactivity of the metalloproteinase-26 in tumoral stroma, n (%)

	Lesion		
MMP-26	Ameloblastoma	AOT	P value
Present	13 (65)	5 (50)	.69
Absent	7 (35)	5 (50)	

AOT, Adenomatoid odontogenic tumor.

DISCUSSION

Although ameloblastoma and AOT are classified by WHO in the same group, formed by epithelial odontogenic tumors with mature fibrous stroma without odontogenic ectomesenchyme, these lesions present distinct biologic behavior. Ameloblastoma is a potentially destructive tumor, whereas AOT presents slow, progressive, and circumscribed growth.[2]

Various factors have been associated with the aggressive behavior of ameloblastomas, such as the increase in the proliferative potential,[15-17] changes in the expression of tumor suppressor genes and their protein products,[18-21] and modifications in cell cycle mechanisms.[22,23] Besides these, other factors have also been investigated in an attempt of better understanding the behavior of these tumors, such as growth factors,[24] adhesion molecules,[24,25] and changes in stromal components[26] and the expression of metalloproteinases and their inhibitors, tissue inhibitor of metalloproteinases (TIMPs).[24,27-30]

The MMPs play an important role in cell proliferation, angiogenesis, invasion, and metastasis in various human malignant tumors.[12,31-33] In physiologic conditions, MMPs are weakly stained in the tissues, whereas in pathological processes there is overexpression due to the imbalance in the activity of MMPs and TIMPs.[7,10,34]

Some studies have evaluated MMPs expression in mostly distinct pathologies.[35,36] Nonetheless, studies involving cysts and odontogenic tumors are still scarce. Among the MMPs, collagenase-1 (MMP-1) and gelatinases (MMP-2 and -9) seem to play an important role in the development of these lesions, actively participating in the interactions between epithelial cells and mesenchymal components.

Previous research has confirmed MMP-1, -2, and -9 expression in ameloblastomas and odontogenic myxomas, suggesting that these proteinases are involved in the process of ECM degradation and contribute to the local invasiveness of these tumors. The inhibition of MMP-2 activity was also related to the decrease in local invasiveness in ameloblastomas.[27-29,37] In addition to the high expression of MMP-2 and -9, the aggressive behavior of these tumors has also been associated with changes in the expression of vascular endothelial growth factor and E-cadherin.[24] Silveira et al.[38] also verified greater expression of MMP-1, -2 and -9 in the mesenchymal cells of nonsyndrome odontogenic keratocysts than in radicular, residual, and dentigerous cysts, confirming the participation of these enzymes in this lesion growth, as well as justifying that the first lesions are more aggressive than the latter three. Kumamoto et al.[27] detected strong expression of MMP-1, -2, and -9 and TIMP-1 and -2 in mesenchymal components of dental follicles and dental papillae and in stromal cells of ameloblastomas. Those findings suggest that these molecules might play a role in regulating tumor progression in ameloblastomas as well as in regulating developmental processes in tooth germs.

Studies involving matrilysins and odontogenic tumors are even rarer. Cavalcante et al.[14] evaluated the expression of MMP-7 and -26 in syndrome and nonsyndrome odontogenic keratocysts and observed stronger epithelial expression in cases associated with Gorlin syndrome than in nonsyndrome cases, which may explain the more aggressive behavior of the keratocysts associated with this syndrome.

In the present study, most cases of ameloblastoma and AOT showed strong expression of MMP-7 and -26 in the epithelium as well as the stroma, which suggests the participation of these MMPs in tissue remodeling.

Matrilysins may degrade a variety of ECM substrates. MMP-7 cleaves fibronectin, gelatin, elastin, laminin, and type IV collagen.[39] Moreover, this matrilysin also acts in non-ECM substrates, such as tumor necrosis factor α, Fas ligand, E-cadherin, and pro–α-defensin.[7] MMP-26 also shows proteolytic activity over various components of ECM, including fibronectin, type IV collagen, vitronectin, gelatin, and fibrino-

gen,[7,40] and in noncomponents of this matrix, such as fibrinogen and inactive serpin.[41,42]

Because matrilysins degrade ECM proteins, their primary function has been presumed to be tissue remodeling. However, their action on other substrates, such as growth factors, growth factor protein bindings, and adhesion molecules,[7,29] may modulate cell behavior,[43] which might make matrilysins to play a central role in tumor invasion and metastasis.[44] Additionally, MMP-7 activates latent forms of other MMPs (proMMP-1, -2, and -9) and MMP-26 activates MMP-9.[39,45] Because gelatinases are involved in tumor invasion processes and metastasis,[9,24,28-30,33,46,47] the present findings indirectly suggest the participation of MMP-7 and -26 in invasive processes in ameloblastomas, because their strong immunoexpression can be correlated with the activation of MMPs -2 and -9.

Some MMPs are expressed by tumor and host cells.[48] Expression of MMP-7 has been described in epithelial cells, myofibroblasts, macrophages, and endothelial cells.[48,49] Cloned MMP-26 was expressed by macrophages and fibroblasts in vivo and in culture, suggesting that this MMP may contribute to both physiologic processes of tissue remodeling and various benign skin disorders.[50] MMP-26 expression was shown in normal tissues of endometrium, placenta, and kidney.[45] Furthermore, up-regulation of these matrilysins was associated with tumors of epithelial origin.[31,44] In the present study, expression of these matrilysins was shown in both tumor and stromal cells. MMP-7 was evident in epithelial cells, fibroblasts, and endothelial cells of both tumors and in inflammatory cells of the ameloblastomas. And MMP-26 was observed in epithelial cells, fibroblasts, and endothelial cells in both ameloblastomas and AOTs.

Even though there was neither association between MMP staining and the studied lesions nor significant difference between medians of MMPs in the epithelium, our results, when analyzed as a whole, suggest that stromal cells from both studied tumors are capable of producing MMPs with more or less efficiency depending to the studied MMP. That suggests that these enzymes can potentialize the action of epithelium-produced MMPs.

The literature agrees with the role of the stromal microenvironment in tumoral progression, showing evidence of cooperation or synergy between neoplastic cells and stromal fibroblasts in MMP production.[48,51] According to Lynch and Matrisian,[52] MMPs of either tumoral or stromal origin may process cell surface molecules, proteins, or growth factors and cytokines stored in the EMC, causing changes in the microenvironment and thereby favoring tumor growth, migration, invasion, angiogenesis, and selection of cell clones

resistant to apoptosis. Accordingly, those authors believe that MMPs can be used as a means of communication between tumor and stromal cells.

In addition, changes in stromal components may occur due to an imbalance in cytokines, resulting in changes that may ease the transdifferentiation of fibroblasts into myofibroblasts (MFs). MFs are specialized stromal cells that display a hybrid phenotype between fibroblasts and smooth muscle cells.[53] Earlier studies have identified the presence of these cells in neoplasms,[53,54] including odontogenic tumors,[55] relating them to the biologic behavior of these lesions. MFs were identified in ameloblastomas,[55-57] and a high rate of these cells was observed in more aggressive tumors, such as solid ameloblastomas and odontogenic keratocysts.[55] MFs may produce high levels of MMP-2, and the intensive presence of these cells and gelatinases in solid ameloblastomas has been associated with disruption of cortical bone and increased aggressiveness of these tumours.[26]

From our findings, it is plausible to conclude that the expression of these matrilysins suggests their participation in the process of tissue remodeling and ameloblastoma and AOT growth, but this expression does not relate to the their distinct patterns of aggressiveness. However, these matrilysins may indirectly act through the activation of other MMPs associated with changes in the stromal components, which could contribute to the greater aggressiveness of ameloblastomas. We therefore believe that further studies investigating the expression of MMPs and their relationship to stromal components, as well as the use of other techniques, such as zymography, should be undertaken in an attempt to better understand the role and influence of these enzymes in the behavior of the studied tumors.

REFERENCES

1. Jing W, Xuan M, Lin Y, Wu L, Liu X, Zheng W, et al. Odontogenic tumours: a retrospective study of 1642 cases in a Chinese population. Int J Oral Maxillofac Surg 2007;36:20-5.
2. Gardner DG, Heikinheimo K, Shear M, Philipsen HP, Coleman H. Ameloblastomas. In: Barnes L, Eveson JW, Reichart P, Sidransky S, editors. World Health Organization classification of tumours: pathology and genetics of head and neck tumours. Lyon: IARC; 2005. p. 296-300.
3. Santos JN, Pereira Pinto L, Figueredo CR, Souza LB. Odontogenic tumors: analysis of 127 cases. Pesqui Odontol Bras 2001;15:308-13.
4. Olgac V, Koseoglu BG, Aksakalli N. Odontogenic tumors in Istanbull: 527 cases. Br J Oral Maxillofac Surg 2006;44:386-8.
5. Philipsen HP, Reichart PA, Siar CH, Ng KH, Lau SH, Zhang X, et al. An updated clinical and epidemiological profile of the adenomatoid odontogenic tumour: a collaborative retrospective study. J Oral Pathol Med 2007;36:383-93.
6. Egebland M, Werb Z. New functions for the matrix metalloproteinases in cancer progression. Nat Rev Cancer 2002;2:161-74.
7. Nagase H, Visse R, Murphy G. Structure and function of matrix metalloproteinases and TIMPs. Cardiovasc Res 2006;69:562-73.

8. Page-McCaw A, Ewald AJ, Werb Z. Matrix metalloproteinases and the regulation of tissue remodelling. Nat Rev Mol Cell Biol 2007;8:221-33.

9. Franchi A, Santucci M, Masini E, Sardi I, Paglierani M, Gallo O. Expression of matrix metalloproteinase 1, matrix metalloproteinase 2, and matrix metalloproteinase 9 in carcinoma of head and neck. Cancer 2002;95:1902-10.

10. Pereira ALA, Veras SSL, Silveira EJD, Seabra FRG, Pinto LP, Souza LB, et al. O papel das proteínas da matriz extracelular e das metaloproteinases em carcinomas de cabeça e pescoço: uma atualização bibliográfica. Rev Bras Otorrinolaringol 2005;71: 81-6.

11. Marchenko GN, Marchenko ND, Leng J, Strongin AY. Promoter characterization of the novel human matrix metalloproteinase-26 gene: regulation by the T-cell factor-4 implies specific expression of the gene in cancer cells of epithelial origin. Biochem J 2002;363:253-62.

12. de Vicente JC, Lequerica-Fernández P, Santamaría J, Fresno MF. Expression of MMP-7 and MT1-MMP in oral squamous cell carcinoma as predictive indicator for tumor invasion and prognosis. J Oral Pathol Med 2007;36:415-24.

13. Liu D, Nakanoa J, Ishikawaa S, Yokomisea H, Uenob M, Kadotac K, et al. Overexpression of matrix metalloproteinase-7 (MMP-7) correlates with tumor proliferation, and a poor prognosis in nonsmall cell lung cancer. Lung Cancer 2007;58:384-91.

14. Cavalcante RB, Pereira KMA, Nonaka CFW, Nogueira RLM, Souza LB. Immunohistochemical expression of MMP 1, 7, and 26 in syndrome and nonsyndrome odontogenic keratocysts. Oral Surg Oral Med Oral Pathol Oral Radiol Oral Endod 2008; 106:99-105.

15. Meer S, Galpin JS, Altini M, Ali N. Proliferating cell nuclear antigen Ki67 immunoreactivity in ameloblastomas. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003;95:213-21.

16. Thosaporn W, Iamaroon A, Pongsiriwet S, Ng KH. A comparative study of epithelial cell proliferation between the odontogenic keratocyst, orthokeratinized odontogenic cyst, dentigerous cyst, and ameloblastoma. Oral Dis 2004;10:22-6.

17. Payeras MR, Sant'Ana Filho M, Lauxen IS, Barbachan JJD. Quantitative analysis of argyrophilic nucleolar organizer regions and epidermal growth factor receptor in ameloblastomas. J Oral Pathol Med 2007;36:99-104.

18. Barreto DC, Bale AE, De Marco, Gomez RS. Immunolocalization of PTCH protein in odontogenic cysts and tumors. J Dent Res 2002;81:757-60.

19. Sandra F, Nakamura N, Kanematsu T, Hirata M, Ohishi M. The role of MDM2 in proliferative activity of ameloblastoma. Oral Oncol 2002;38:153-7.

20. Kumamoto H, Izutsu T, Ohki K, Takahashi N, Ooya K. p53 gene status and expression of p53, MDM2, and p14ARF proteins in ameloblastoma. J Oral Pathol Med 2004;33:292-9.

21. Scheper MA, Chaisuparat R, Nikitakis NG, Sauk JJ. Expression and alterations of the PTEN/AKT/mTOR pathway in ameloblastomas. Oral Dis 2008;14:561-8.

22. Kumamoto H, Kinouchi Y, Ooya K. Telomerase activity and telomerase reverse transcriptase (TERT) expression in ameloblastomas. J Oral Pathol Med 2004;33:292-9.

23. Kumamoto H, Ooya K. Expression of tumor necrosis factor α, TNF-related apoptosis-inducing ligand, and their associated molecules in ameloblastomas. J Oral Pathol Med 2005;34:287-94.

24. Zhong M, Li ZJ, Wang J, Yue YL, Bao G. The study of the invasive biologic behavior of ameloblastoma. Zhonghua Kou Qiang Yi Xue Za Zhi 2004;39:45-8.

25. Andrade ESS, Miguel MC, Freitas RA, Pereira Pinto L, Souza LB. Immunoexpression of integrins in ameloblastoma, adenoma-

26. Fregnani ER, Sobral LM, Alves FA, Soares FA, Kowalski LP, Coletta RD. Presence of myofibroblasts and expression of matrix metalloproteinase-2 (MMP-2) in ameloblastomas correlate with rupture of the osseous cortical. Pathol Oncol Res 2009;15:231-40.

27. Kumamoto H, Yamauchi K, Yoshida M, Ooya K. Immunohistochemical detection of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) in ameloblastomas. J Oral Pathol Med 2003;32:114-20.

28. Zhong M, Han YP, Wang J, Li ZJ, Bao G, Yue YL. Expression of matrix metalloproteinases and tissue inhibitor of metalloproteinase in ameloblastoma. Shanghai Kou Qiang Yi Xue 2003;12: 427-31.

29. Pinheiro JJ, Freitas VM, Moretti AI, Jorge AG, Jaeger RG. Local invasiveness of ameloblastoma. Role played by matrix metalloproteinases and proliferative activity. Histopathology 2004;45: 65-72.

30. Wang A, Zhang B, Huang H, Zhang L, Zeng D, Tao Q, et al. Suppression of local invasion of ameloblastoma by inhibition of matrix metalloproteinase-2 in vitro. BMC Cancer 2008;8:1-9.

31. Stamenkovic I. Matrix metalloproteinases in tumor invasion and metastasis. Semin Cancer Biol 2000;10:415-33.

32. Polette M, Nawrocki-Raby B, Gilles C, Clavel C, Birembaut P. Tumour invasion and matrix metalloproteinases. Crit Rev Oncol Hematol 2004;49:179-86.

33. Tang C, Tan T, Fu W, Yang R. Involvement of matrix metalloproteinase-9 in stromal cell-derived factor-1/CXCR4 pathway of lung cancer metastasis. Carcinogenesis 2008;29:35-43.

34. Verma RP, Hansch C. Matrix metalloproteinases (MMPs): chemical-biological functions and (Q) SARs. Bioorg Med Chem 2007;15:2223-68.

35. Gapski R, Hasturk H, Van Dyke TE, Oringer RJ, Wang S, Braun TM, et al. Systemic MMP inhibition for periodontal wound repair: results of a multi-centre randomized-controlled clinical trial. J Clin Periodontol 2009;36:149-56.

36. Sands MF, Ohtake PJ, Mahajan SD, Takyar SS, Aalinkeel R, Fang YV, et al. Tissue inhibitor of metalloproteinase-1 modulates allergic lung inflammation in murine asthma. Clin Immunol 2009;130:186-98.

37. Bast BT, Pogrel MA, Regezi JA. The expression of apoptotic proteins and matrix metalloproteinases in odontogenic myxomas. J Oral Maxillofac Surg 2003;61:1463-6.

38. Silveira EJD, Piva MR, Galvão HC, Souza LB, Freitas RA. Participação das metaloproteinases da matriz na etiopatogenia dos cistos odontogênicos. J Bras Patol Med Lab 2007;43:203-9.

39. Wilson CL, Matrisian LM. Matrilysin: an epithelial matrix metalloproteinase with potentially novel functions. Int J Biochem Cell Biol 1996;28:123-36.

40. Li M, Yamamoto H, Adachi Y, Maruyama Y, Shinomura Y. Role of matrix metalloproteinase-7 (matrilysin) in human cancer invasion, apoptosis, growth, and angiogenesis. Exp Biol Med (Maywood) 2006;231:20-7.

41. Park HI, Ni J, Gerkema FE, Liu D, Belozerov VE, Sang QX. Identification and characterization of human endometase (matrix metalloproteinase-26) from endometrial tumor. J Biol Chem 2000;275:20540-4.

42. Zhao YG, Xiao AZ, Newcomer RG, Park HI, Kang T, Chung LW, et al. Activation of pro-gelatinase B by endometase/matrilysin-2 promotes invasion of human prostate cancer cells. J Biol Chem 2003;278:15056-64.

43. Sires UI, Murphy G, Baragi VM, Fliszar CJ, Welgus HG, Senior RM. Matrilysin is much more efficient than other matrix metalloproteinases in the proteolytic inactivation of a1-antitrypsin. Biochem Biophys Res Commun 1994;204:613-20.

44. Kerkela E, Saarialho-Kere U. Matrix metalloproteinases in tumor progression:focus on basal and squamous cell skin cancer. Exp Dermatol 2003;12:109-25.

45. Kuula H, Salo T, Pirila E, Hagstrom J, Luomanen M, Gutierrez-Fernandez A, et al. Human b-defensin-1 and -2 and matrix metalloproteinase-25 and -26 expression in chronic and aggressive periodontitis and in peri-implantitis. Arch Oral Biol 2008; 53:175-86.

46. Uría JA, López-Otín C. Matrilysin-2, a new matrix metalloproteinase expressed in human tumors and showing the minimal domain organization required for secretion, latency, and activity. Cancer Res 2000;60:4745-51.

47. de Vicente JC, Fresno MF, Villalain L, Vega JA, Vallejo GH. Expression and clinical significance of matrix metalloproteinases-2 and matrix metalloproteinases-9 in oral squamous cell carcinoma. Oral Oncol 2005;41:283-93.

48. Noël A, Jost M, Maquoi E. Matrix metalloproteinases at cancer tumor-host interface. Semin Cell Dev Biol 2008;19:52-60.

49. Sier CF, Hawinkels LJ, Zijlmans HJ, Zuidwijk K, de Jonge-Muller ES, Ferreira V, et al. Endothelium specific matrilysin (MMP-7) expression in human cancers. Matrix Biol 2008; 27:267-71.

50. Skoog T, Ahokas K, Orsmark C, Jeskanen L, Isaka K, Saarialho-Kere U. MMP-21 is expressed by macrophages and fibroblasts in vivo and in culture. Exp Dermatol 2006;15:775-83.

51. DeClerck YA. Interactions between tumour cells and stromal cells and proteolytic modification of the extracellular matrix by metalloproteinases in cancer. Eur J Cancer 2000;36:1258-68.

52. Lynch CC, Matrisian LM. Matrix metalloproteinases in tumor-host cell communication. Differentiation 2002;70:561-73.

53. Desmouliere A, Guyot C, Gabbiani G. The stroma reaction myofibroblast: a key player in the control of tumor cell behavior. Int J Dev Biol 2004;48:509-17.

54. Powell DW, Adegboyega PA, Di Mari JF, Mifflin RC. Epithelial cells and their neighbors I. Role of intestinal myofibroblasts in development, repair, and cancer. Am J Physiol Gastrointest Liver Physiol 2005;289:G2-7.

55. Vered M, Shohat I, Buchner A, Dayan D. Myofibroblasts in stroma of odontogenic cysts and tumors can contribute to variations in the biological behavior of lesions. Oral Oncol 2005; 41:1028-33.

56. Rothouse LS, Majack RA, Fay JT. An ameloblastoma with myofibroblasts and intracellular septate junctions. Cancer 1980; 45:2858-63.

57. Smith SM, Bartov SA. Ameloblastoma with myofibroblasts: first report. J Oral Pathol 1986;15:284-6.

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