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# Immunohistochemical analysis of COX-2 expression in dentigerous cyst, keratocystic odontogenic tumor and ameloblastoma: A comparative study

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## ABSTRACT

**Background:** Cyclo-oxygenase-2 (COX-2) is an early response gene that is induced by growth factors, oncogenes and carcinogens and its expression is increased in various tumors. Increased expression of COX-2 plays a significant role in the development and growth of tumors by interfering in biological processes such as cell division, cellular immunity, cell adhesion, apoptosis, and angiogenesis. This study aimed to investigate the immunohistochemical expression of COX-2 in keratocystic odontogenic tumor (KOT) in comparison with ameloblastoma and dentigerous cyst with regards to different clinical behavior and histopathological features of these lesions.

**Materials and Methods:** Paraffined blocks of 45 cases including 15 cases of dentigerous cyst, 15 cases of KOT and 15 cases of ameloblastoma were stained with immunohistochemical method for COX-2. Five high-power fields of each sample were evaluated to determine the percentage of stained cells and the intensity of staining. Degree of immunoreactivity was obtained from the sum of two. Statistical evaluation was performed by the Kruskal-Wallis and ANOVA Mann-Whitney test ($P < 0.05$).

**Results:** Overexpression of COX-2 in ameloblastoma and KOT was observed compared with dentigerous cyst ($P < 0.001$). However, no significant difference was observed between the expression of COX-2 in ameloblastoma and KOT ($P = 0.148$).

**Conclusion:** The COX-2 expression in odontogenic tumors such as ameloblastoma and cystic neoplasm with aggressive behavior such as KOT increases. However, it does not seem that COX-2 affects the development and growth of cysts with noninvasive behavior like dentigerous cyst.

**Key Words:** Ameloblastoma, cyclo-oxygenase-2, dentigerous cyst, immunohistochemistry, keratocystic odontogenic tumor

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## INTRODUCTION

Odontogenic cysts and tumors are developed because of the abnormalities that occur during odontogenesis. Therefore, they are considered as developmental disorders of odontogenic tissues. Odontogenic cysts are more common in the oral cavity, but odontogenic tumors are less likely to be seen.[1] The epithelial layer of dentigerous cyst may transform into ameloblastoma, squamous cell carcinoma or intraosseous mucoepidermoid carcinoma. In 2005, the World Health Organization working group considered the parakeratinized odontogenic keratocyst (OKC) as a cystic neoplasm and suggested the more appropriate term of "keratocystic odontogenic tumor (KOT)." It seems that OKC has neoplastic potential. Although, KOT has particular histopathological features and clinical course, its developmental mechanisms and

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biological behavior is different from dentigerous cyst. Most authors agree that dentigerous cyst grows in size because of the increased osmotic pressure within the lumen of the cyst. However, the growth of KOT may be due to unknown inherited factors in epithelium or enzymatic activity of fibrous connective tissue of cystic wall. Epithelial dysplasia and epidermoid carcinoma may rarely be created in that. Findings are inconsistent regarding the tendency toward the ameloblastomatous transformation.[2,3] Ameloblastoma, as the most common odontogenic tumor in many countries such as Iran, Brazil and China, has slow growth, local invasion, and high recurrence rate.[2,4]

Cyclo-oxygenase (COX) catalyzes the synthesis of prostaglandins from arachidonic acid. Studies have revealed that COX-2 levels increase in various tumors, especially tumors involving the esophagus, oral cavity, lung, and head and neck.[5-9] The mechanism of overexpression of this enzyme in tumor samples is still unknown. It is also shown that increased expression of COX-2 by interfering in biological processes such as cell proliferation, cell adhesion, cellular immunity, apoptosis and angiogenesis, plays an important role in growth and development of tumor.[10] Mendes *et al*.[10] in a review on COX-2 expression in the head and neck tumors found that the expression level of COX-2 increases in various head and neck tumors and benign neoplasms with aggressive behavior, such as KOT,[11,12] but the mechanism of this increase is still unknown. Furthermore, studies on the molecular markers related to biological behavior of tumors play an important role in understanding the associated molecular mechanism and prediction of the clinical behavior of these tumors. This information could lead to the development of new therapeutic pathways such as molecular targeted therapies and treatments tailored to patients.[10] Therefore, considering the different biological behavior of dentigerous cyst, KOT and ameloblastoma, percentages of different recurrence rate after treatment and their different natures, we decided to assess the expression of COX-2 in these lesions.

## MATERIALS AND METHODS

### Sampling

This study was approved by the Ethics Committee of Babol University of Medical Sciences (no. 1466). Forty-five formalin fixed paraffin embedded specimens (15 cases of ameloblastoma, 15 cases of KOTs, 15 cases of dentigerous cyst) were withdrawn from the archives of Department of Oral Pathology, Babol Dental School (2003-2013). It should be noted that considering the effect of inflammation on the expression of COX-2, in this study, samples of noninflammatory lesions were used. 3 μm sections from each block were prepared and stained with hematoxylin and eosin to confirm the diagnosis. Samples from recurrent lesions and cases of nevoid basal cell carcinoma syndrome were excluded. Colon carcinoma was used as a positive control. Negative controls included omission of the primary antibody.

### Immunohistochemistry

Immunohistochemical staining was performed according to Novolink™ Polymer Detection System (Leica Biosystems Newcastle Ltd., UK, Product NO: RE7140-K). 3 μ sections were prepared from paraffin embedded blocks and were placed on silane-coated slides. Samples were deparaffinized in xylene and then hydrated in graded alcohol.

Deparaffinized slides were placed in citrate buffer (pH = 6.2) for antigen retrieval and were transferred to microwave and once the buffer reached the boiling point, it was kept in this state for 15 min. Internal peroxidase activity was blocked using 3% hydrogen peroxide. To reduce nonspecific antibody bond, the protein block solution was used. Following this, samples were covered using a primary antibody (rabbit polyclonal anti-COX-2/COX-2 antibody, immunoglobulin G Isotype, ab15191, Abcam, USA) with dilution of 1/500. The samples were washed with tris-buffered saline. After that, postprimary block solution was used to increase the penetration of secondary antibody solution. Then, sections were covered with secondary antibody for 30 min. Solution of diaminobenzidine was used as the chromogen. This solution reacts with peroxidase, produces brown color. It clarifies the bond peroxidase areas. Finally, hematoxylin solution was used as counterstain. The slides were dehydrated in graded alcohol, cleaned in xylene, and covered with a coverslip.

### Evaluation of cyclo-oxygenase-2-2 immunostaining

Prepared slides were observed by two independent pathologists using a light microscope (Olympus BX41, Tokyo, Japan) with equal ×400 magnification. Five high-power fields were selected from each sample and a minimum of 700 epithelial cells were evaluated. Percentage of positive cells examined was scored as 0 (negative), 1 (<25%), 2 (25-50%),

3 (51-75%), and 4 (75-100%). Staining intensity was graded as 0 (negative), 1 (weak), 2 (moderate), 3 (strong).[12] Smooth muscle cells in the sample were used as an internal positive control.[13] The degree of immunoreactivity or total score was obtained by the sum of scores of percentage of positive cells and staining intensity score.[13]

### Statistical analysis

To compare the groups in terms of the degree of immunoreactivity, Kruskal-Wallis and ANOVA test were used. The comparison of COX-2 expression between the two groups was performed using the Mann-Whitney test. The difference between groups was considered statistically significant at $P < 0.05$.

## RESULTS

This study was carried out on 45 specimens, including 15 cases of dentigerous cyst, (13 male and 2 female with an average age of 10.86 ± 23.20 years) and 15 cases of KOT (4 male patients and 11 female patients with an average age of 10.12 ± 30.87 years) and 15 cases of ameloblastoma (3 male patients and 12 female patients with an average age of 9.14 ± 29 years). Locations of Lesions are shown in Table 1.

The score of staining intensity for KOT shows minimum difference between score 1 and score 2. However, 66.66% of dentigerous cysts were not stained [Table 2 and Figure 1].

Kruskal-Wallis test represented a significant difference between three groups in terms of staining intensity ($P < 0.001$).

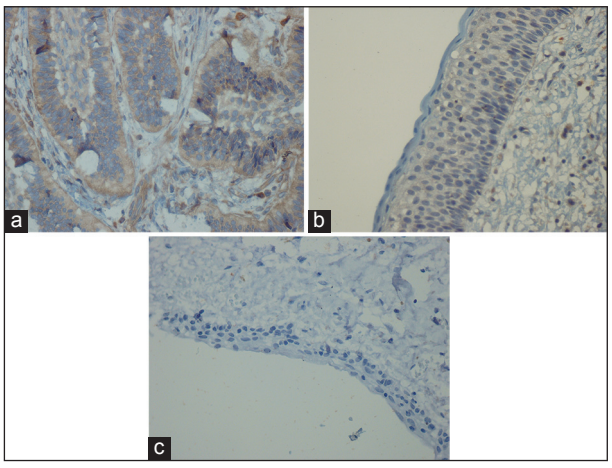


**Figure 1:** Expression of cyclo-oxygenase-2 in ameloblastoma (a) in keratocystic odontogenic tumor (b) and dentigerous cyst (c) (immunohistochemical staining, ×400).

The staining intensity of COX-2 in ameloblastoma and KOTs increased significantly when compared with dentigerous cyst ($P < 0.001$ and $P < 0.001$). There was no significant difference between ameloblastoma and KOTs ($P = 0.148$).

Results related to the percentage of stained cells are shown in Table 3.

There was a significant difference between the percentages of stained cells between three groups ($P < 0.001$) [Figure 2].

**Table 1: Distribution of location of lesions for dentigerous cyst, KOT and ameloblastoma**

| Location | Specimen type | | |
|---|---|---|---|
| | Dentigerous cyst | KOT | Ameloblastoma |
| | Percentage (no.) | Percentage (no.) | Percentage (no.) |
| Anterior mandible | 6.66 (1) | 0 (0) | 0 (0) |
| Anterior maxilla | 6.66 (1) | 0 (0) | 0 (0) |
| Posterior mandible | 73.33 (11) | 80 (12) | 73.33 (11) |
| Posterior maxilla | 13.33 (2) | 20 (3) | 26.66 (4) |
| Total | 100 (15) | 100 (15) | 100 (15) |

KOT: Keratocystic odontogenic tumor.

**Table 2: The results of immunohistochemical staining in terms of staining intensity in three study groups**

| Specimen type | Score | | | |
|---|---|---|---|---|
| | Score 0 | Score 1 | Score 2 | Score 3 |
| | Percentage (no.) | Percentage (no.) | Percentage (no.) | Percentage (no.) |
| Dentigerous cyst | 66.66 (10) | 33.33 (5) | 0 (0) | 0 (0) |
| KOT | 0 (0) | 40 (6) | 46.66 (7) | 13.33 (2) |
| Ameloblastoma | 0 (0) | 13.33 (2) | 60 (9) | 26.6 (4) |

KOT: Keratocystic odontogenic tumor.

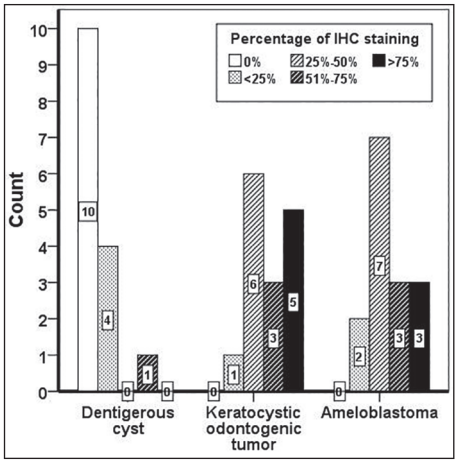


**Figure 2:** Comparison of percentage of stained cells in three groups and the score of each group.

There was a significant difference between the percentage of stained cells in ameloblastoma and KOT compared with dentigerous cyst ($P < 0.001$). However, the percentage of stained cells in ameloblastoma and KOT showed no significant difference ($P = 0.148$).

Another result is that a significant difference was observed between the degrees of immunoreactivity between the three groups ($P < 0.001$) [Figure 3].

Mean of degree of immunoreactivity or total score, in each group and its comparison between three groups is shown in Figure 3.

In comparing the degree of immunoreactivity between ameloblastoma and dentigerous cyst and in comparison between dentigerous cyst and KOT, significant differences were observed ($P < 0.001$ and $P < 0.001$), but no significant difference was observed in degree of immunoreactivity between ameloblastoma and KOT ($P = 0.07$). The results related to the degree of immunoreactivity are reported in Table 4 and Figure 4.

## DISCUSSION

The results of this study showed a higher level expression of COX-2 in ameloblastoma and KOTs in comparison to dentigerous cyst. It confirms the role of COX-2 in the invasive behavior of odontogenic lesions such as ameloblastoma and KOT when compared to the lesions with less aggressive clinical behavior such as dentigerous cyst. Mendes *et al*.[11,12] in their study

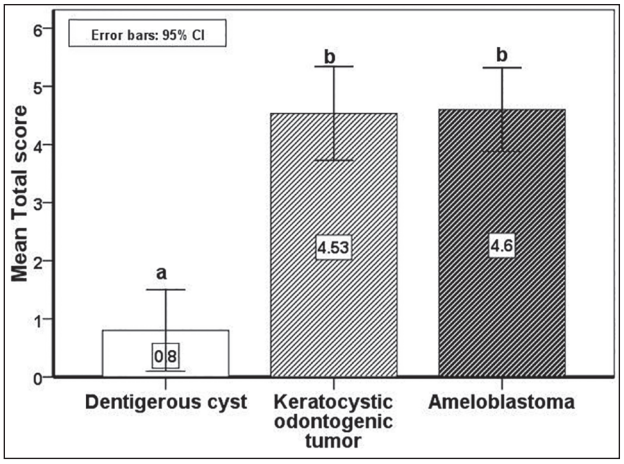


**Figure 3:** Average degree of immunoreactivity between the three groups.

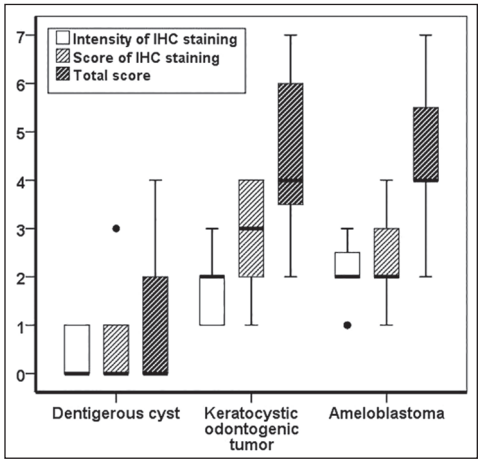


**Figure 4:** Comparison of three groups in terms of staining intensity score, percentage of stained cells and the degree of immunoreactivity (total score).

**Table 3: Results of immunohistochemical staining with regards to the percentage of stained cells in three study groups**

| Specimen type | Score | | | | |
|---|---|---|---|---|---|
| | Score 0 | Score 1 | Score 2 | Score 3 | Score 4 |
| | Percentage (no.) | Percentage (no.) | Percentage (no.) | Percentage (no.) | Percentage (no.) |
| Dentigerous cyst | 66.66 (10) | 26.66 (4) | 0 (0) | 6.66 (1) | 0 (0) |
| KOT | 0 (0) | 6.66 (1) | 40 (6) | 20 (3) | 33.33 (5) |
| Ameloblastoma | 0 (0) | 13.33 (2) | 46.66 (7) | 20 (3) | 20 (3) |

KOT: Keratocystic odontogenic tumor.

**Table 4: Results of immunohistochemical staining in terms of total score in three study groups**

| Specimen type | Total score | | | | | | |
|---|---|---|---|---|---|---|---|
| | Score 0 | Score 2 | Score 3 | Score 4 | Score 5 | Score 6 | Score 7 |
| | Percentage (no.) | Percentage (no.) | Percentage (no.) | Percentage (no.) | Percentage (no.) | Percentage (no.) | Percentage (no.) |
| Dentigerous cyst | 66.66 (10) | 26.66 (4) | 0 (0) | 6.66 (1) | 0 (0) | 0 (0) | 0 (0) |
| KOT | 0 (0) | 6.66 (1) | 20 (3) | 26.66 (4) | 13.33 (2) | 26.66 (4) | 6.66 (1) |
| Ameloblastoma | 0 (0) | 6.66 (1) | 6.66 (1) | 40 (6) | 20 (3) | 20 (3) | 6.66 (1) |

KOT: Keratocystic odontogenic tumor.

confirmed the overexpression of COX-2 in KOT and its relationship with the aggressive behavior. Overexpression of COX-2 in a variety of human tumors including head and neck and esophageal cancers has been reported.[8,14,15] The importance of COX-2 was first proved in laboratory rats suffering from adenomatoid polyposis. It was a hereditary disorder and lead to the gastrointestinal tract cancer. In this disease, the lack of activity of COX-2 occurs by genetic deletion or selective enzyme inhibition in intestinal polyps.

Recent studies have shown the COX-2 overexpression in malignant and premalignant lesions. Furthermore, genetic evidences based on the frequency of transcription of COX-2 in tumorogenesis are available.[7,8,16,17] Further evidences about the importance of COX-2 in tumorogenesis, reported by Liu *et al*., showed that increased selective COX-2 expression in mammary glands of laboratory rats cause tumorogenesis.[18] Chemopreventive effects of COX-2 selective inhibitors and its inhibitory effect on tumor growth and metastasis and enhancement of the anticancer effects of radiotherapy and chemotherapy in experimental animals[19] and human models[20] indicate the role of this protein in tumorogenesis. Expression of COX-2 is a key factor in regulating the expression of prostaglandin E2.[21,22] Synthesis of prostaglandin E2 needs conversion of arachidonic acid to prostaglandin H2 by COX-1 and COX-2. COX-2 levels are negligible in normal conditions, but it increases by pathological stimuli. Increased expression of prostaglandin is regulated by COX-2, which can cause increased cell proliferation, promotion of angiogenesis and inhibition of the immunoreactivity.[18,23] It has been established that interleukin-1 (IL-1) alpha stimulates prostaglandin E2 production in fibroblasts of KOT. Ogata *et al*. showed that IL-1 alpha increases COX-2 expression and stimulates production of prostaglandin E2 in fibroblasts.[21] Various studies have shown that prostaglandin E2 inhibits tumor necrosis factor. Furthermore, prostaglandin E2 induces IL-10 that the latter is a cytokine with inhibitory effects on the immune system. It also appears that increased expression of COX-2, changes cell adhesion and response to regulatory signals and also it inhibits apoptosis.[7,23,24]

Stolina *et al*.[25] showed that inhibition of COX-2 regulates infiltration of lymphocytes and reduces tumor growth. They also observed the repeat of transcription of monoclonal antibody for prostaglandin E2 in laboratory rats treated with COX-2 inhibitors. This repeat of transcription leads to reduced tumor growth and a significant reduction in the secretion of IL-10 and 12. Given that COX-2 regulates prostaglandin E2, it is considered as a major inducer of IL-10 (cytokine with inhibitory effects on the immune system). They hypothesized that inhibition of COX-2, leads to antitumor response, by decreasing the production of this powerful cytokine that reduces immunity.[25]

In this study, increased levels of COX-2 in ameloblastoma and KOT compared with dentigerous cyst were found. In another study, after evaluation of 116 samples of KOT, Mendes *et al*. have reported overexpression of COX-2 in 83 samples.[12]

Cecim *et al*.[26] also observed the overexpression of COX-2 in ameloblastoma. It was shown that it has a significant association with β-catenin and cyclin-D1 expression in the neoplastic cells. They suggested that intracellular markers such as COX-2 may affect local invasion of ameloblastoma. It is in agreement with our results in which we found its overexpression in ameloblastoma with aggressive behavior in comparison with dentigerous cyst that has nonaggressive behavior. Driemel *et al*.[27] observed higher expression of COX-2 in ameloblastoma (82%) compared with KOT (33%). However, recurrence rate of KOT was much higher than ameloblastoma. They concluded that high recurrence rate of KOTs compared with ameloblastoma is due to insufficient extent of resection and it is not predictable with evaluation of cellular markers such as COX-2.

Although COX-2 has rarely been studied to assess odontogenic lesions, according to the results of previous studies and available data on the proven role of COX-2 in tumorogenesis, it can be suggested that COX-2 is a major acting marker in aggressive behavior of KOT and ameloblastoma.

## CONCLUSION

According to the results of this study, difference in immunohistochemical expression of COX-2 between two tumoral odontogenic lesions, ameloblastoma and KOT, when compared to dentigerous cyst can be attributed to its role in the development of

aggressive behavior in mentioned lesions that are tumoral in nature. On the other hand, similarities between ameloblastoma and KOT, in regard to clinical behavior and recurrence rate after treatment, could explain this result. Therefore, according to the obtained results, perhaps COX-2 can be used in targeted molecular therapy in ameloblastoma and KOT.

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