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Impact of COX2, SOX2, and Nestin Expression on Behavior of Dentigerous Cysts, Odontogenic Keratocysts, and Dental Follicles: An Immunohistochemical Study

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Abstract

Objective(s): Odontogenic Keratocyst (OKC) and Dentigerous Cyst (DC) are two common developmental odontogenic cysts affecting jaws. The role of cyclooxygenase-2 (COX2), SRY-related HMG-box gene 2 (SOX2), and Nestin in the invasion and progression of cysts and tumors has been studied. This study aimed to compare the expression of COX2, SOX2, and Nestin markers in DC and OKC. **Methods:** In this descriptive-analytical study, samples, including 80 paraffin blocks (32 DC, 32 OKC, and 16 cases of Dental follicle (DF)), were selected, and Immunohistochemical (IHC) staining using the antibodies for COX2, SOX2, and Nestin markers was performed using the envisioned method. Data was analyzed using the Kruskal-Wallis test at $p<0.05$. **Results:** The highest mean percentage of COX2, SOX2, and Nestin expression was observed in the DC, OKC, and DF, respectively. The only significant difference in COX2 expression was observed between the DF and DC ($P = 0.001$). The differences in SOX2 expression among the DC, OKC, and DF groups were all significant ($P < 0.05$). The only non-significant difference in Nestin expression was between the DF and DC ($P = 0.157$). **Conclusion:** COX2, SOX2, and Nestin can assist in diagnosing different inflammed types of DC and OKC. COX2 may be effective in explaining OKC's aggressive behavior. The expression of COX2 and SOX2 in DC may indicate the potential for tumoral behavior, while in OKC, it might suggest an increased epithelial proliferation rate. The findings related to Nestin expression in OKC suggest that the connective tissue of the cyst wall does not contribute to tumoral behavior and is not associated with odontogenic ectomesenchyme. Assessing molecular marker expression in IHC evaluation can help identify lesion aggressiveness and guide treatment plans to reduce future complications.

Keywords: Odontogenic Keratocyst; Dentigerous Cyst; Dental Follicle; Cyclooxygenase-2 (COX2); SOX2; Nestin

Introduction

Developmental odontogenic cysts originate from remnants of odontogenic epithelium during development [1, 2]. Potential growth, especially neoplastic changes in epithelial odontogenic cysts have been reported in many studies [3, 4].
Dentigerous cyst (DC) is the most prevalent developmental odontogenic cyst, accounting for 25% of jaw cysts [5-9]. It surrounds the crown of an unerupted tooth, attached at the cementoenamel junction [10-12]. Immunohitochemical (IHC) examination may be required in DC, as it often shows overlapping clinical, radiographic, and histopathological features with other odontogenic cysts [13, 14]. Odontogenic keratocyst (OKC), is the second most common developmental odontogenic cyst and was initially classified as a cyst, then reclassified as a Keratocystic Odontogenic Tumor (KOT) by the World Health Organization (WHO) [15] in 2005. However, in 2017, the WHO reversed this decision, reclassifying it as a cyst once again [16]. OKC is notable for its unique clinical and histological characteristics, including high growth potential, significant destructive capability, aggressive behavior, high recurrence rates (ranging from 3% to 60%) [17], and reports of dysplasia in the cyst epithelium [18]. Moreover, definitive diagnosis of OKC relies on its histopathological appearance [19].
Nowadays, numerous biomarkers are proposed for identifying tumor stem cells [20-24], which have also been studied in oral lesions [25, 26]. The expression pattern of COX2 in DC and OKC could be associated with cancer stem cell-mediated tumor initiation (CSC-mediated tumor initiation) processes [27]. Increased COX2 expression has been reported in various tumors [28, 29] and is likely involved in cell proliferation, enhanced angiogenesis, and immune suppression [28, 30, 31]. Previous studies have reported a moderate to high increase in expression of this marker in the epithelial cells of OKC [21, 32, 33]. SOX2 has been studied as a pluripotent marker that is also expressed in multipotent mature cells [34]. Previous studies have shown that SOX2 may

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play a role in the development or recurrence of odontogenic lesions such as ameloblastoma and OKC [35]. Nestin is recognized as a stem cell marker in tumors, with increased expression observed in cultured cells from oral squamous cell carcinoma (OSCC) [36, 37]. Although its exact function is not fully understood, nestin is believed to contribute to cytoskeletal dynamics, particularly during cell development and migration [36].

This study aimed to compare the expression levels of the stem cell markers COX2, SOX2, and Nestin in OKC, DC, and DF, to elucidate the role of stem cells in the potential tumoral behavior of odontogenic cysts.

Methods

This descriptive-analytical study was conducted by reviewing the archived records from the Department of Oral and Maxillofacial Pathology of Shahid Beheshti University of Medical Sciences, Tehran, Iran Between 2008 and 2023. Sample size was calculated based on the study by Cigdem et al. [38], which reported specific means and standard deviations for each lesion. A power of 90%, alpha of 0.05, and allocation ratios of 1:2:2 were considered for DF, DC, and OKC, respectively. Finally, the required total sample size was 80, estimated as 16 DF, 32 DC, and 32 OKC cases (allocation ratio 1:2:2). All slides were reviewed by a pathologist to confirm definitive diagnoses. For each sample, data on gender, age, lesion location, description, and final pathology diagnosis were recorded, along with marker staining percentage and intensity. Samples with insufficient tissue, poor preservation, or incomplete clinical or radiographic data were excluded.

Immunohistochemical staining

Paraffin blocks were sectioned using a microtome to produce 3-micron thick slices, which were placed on Silanized Glass Microscope Slides (Dako code: S300330, Denmark) specifically designed for immunohistochemistry. These slides, which provide better tissue adhesion, help reduce errors related to tissue wrinkling, overlapping, or detachment during the staining process. Then, the IHC staining was performed using the following method: The slides were placed in an oven at 60°C for two hours and then deparaffinized and dehydrated. They were immersed in two containers of 100% xylene, each for five minutes, followed by immersion in containers of 99% ethanol (twice for five minutes each) and 96% ethanol (twice for five minutes each). Afterward, the slides were rinsed with tap water for five minutes and placed in a container of distilled water. Next, a peroxide solution (containing hydrogen peroxide and methanol in a 1:9 ratio) was applied to the slides for five minutes, followed by rinsing with tap water and then placing the slides in distilled water. Then, for antigen retrieval, the slides were boiled for 20 minutes in a Coplin jar containing a buffer (according to the primary antibody concentration in Table 1), and left at room temperature for 10 minutes to cool down. After cooling, they were rinsed with tap water and placed in distilled water. Next, the necessary tissues were circled with a pen and incubated with primary antibodies at specific concentrations (using a diluent solution) for the duration specified in Table 1, in a closed and humid container. After one hour, the slides were placed in a rinsing buffer (containing one part of salt, Tris, hydrochloric acid, and four parts of distilled water) with a pH of 7 for five minutes. Then, the Envision solution was applied to the slides for one hour in the same closed and humid container, followed by a rinsing step.

Table 1- primary antibody concentration

Brand	Catalog number	Name	Time	Buffer	Dilution
Abcam England	Ab52237	Anti-COX2 antibody	90 min	Citrate buffer pH=6	Ab79995 1:100
Abcam England	Ab97959	Anti-SOX2 antibody	90 min	Citrate buffer pH=6	Ab79995 1:100
Abcam England	Ab105389	Anti-Nestin antibody	24 hrs	EDTA pH=9	Ab79995 1:500

After that, one or two drops of DAB (Novocastra, England) (at a ratio of 1 chromogen to 20 substrate) were applied to each slide. After two to three minutes, the samples were examined under a microscope to ensure proper staining (browning of cells by the markers). The slides were then rinsed with tap water for five minutes. The samples were then placed in hematoxylin and lithium carbonate for background tissue staining and rinsed with water for five minutes. They were subsequently dehydrated in graded alcohols and cleared in xylene twice (each for five minutes). Finally, the samples were mounted. After drying, the slides were examined under a light microscope to assess the number of positively stained cells and the intensity of staining.

The positive control for this study was OSCC tissue for COX2 and SOX2, and kidney tissue for Nestin. The negative control consisted of the same tissues without the application of the primary antibodies. Control samples were stained in each step to prevent errors, and if any issues were found, new paraffin blocks were prepared, and the slides were stained again. All these steps were performed by an experienced laboratory technician who was blinded to the samples. Additionally, it is noteworthy that all sample examinations were conducted in collaboration with the Oral and Maxillofacial Pathology Department of Shahid Beheshti Dental School and were approved by the Ethics

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Committee of Shahid Beheshti University of Medical Sciences (Ethics Code: IR.SBMU.RIDS.REC.1395.224). Furthermore, this study adhered to the ethical principles of the Declaration of Helsinki, ensuring responsible use of human data and protection of patient rights, privacy, and confidentiality.

Semiquantitative Evaluation of Markers Expression

COX2 and Nestin showed cytoplasmic staining, while SOX2 exhibited nuclear staining. Marker expression was evaluated (light microscope, E400, Nikon, Japan, 400x magnification) by experienced oral and maxillofacial pathologists (F.M. and S.G.T.) in a blinded assessment.

For the Nestin marker, the number of stained cells was counted among 100 cells and expressed as a percentage [39]. For COX2 and SOX2, 700 epithelial cells in five high-power fields were evaluated and classified on a proportion score [40].

For the SOX2, cells with brown dots in the nucleus were considered stained, and for the COX2 and Nestin, cells with brown dots in the cytoplasm were considered stained. Finally, the obtained percentages were classified according to the following proportion score: [39-41] (Table 2)

Data Analysis Methods

1. Examination of Frequency and Relative Frequency of Scores for the Three Markers in Each of the Three Study Groups:

To compare the rank distribution of each marker among the three study groups, we used the Kruskal-Wallis test. For pairwise comparisons between the study groups, we used the Dunn's Q test with Bonferroni correction.

2. Comparison of the Average Percentage of Stained Cells in the Study Groups:

After verifying the data distribution using the Kolmogorov-Smirnov test and determining that it was not normal, we applied the non-parametric Kruskal-Wallis H test as the appropriate statistical test. All statistical tests were applied at a significance level of 0.05.

Table 2- Proportion score

Marker	Score	Staining Percentage
COX2	0	0%
	1+	1-25%
	2+	26-50%
	3+	51-75%
	4+	76% and above
SOX2	0	0%
	1+	1-10%
	2+	11-50%
	3+	51% and above
Nestin	0	0%
	1+	1-30%
	2+	31-60%
	3+	61% and above

Results

A total of 80 samples were analyzed, including 32 DC (16 non-inflammatory and 16 inflammed), 32 OKC (16 non-inflammatory and 16 inflammed), and 16 DF (8 non-inflammatory and 8 thickened). The highest mean age was for the OKC group (32 ± 11), while the lowest was for the DF group (16 ± 5). DC and OKC were more common in males, while DF had an equal distribution between males and females. The posterior mandible was the most common site for all types of lesions, while the anterior mandible was the the least frequent site for lesion occurrence overall (Table 3).

Table 3- Demographic characteristics and location distribution of study groups.

Lesion	Type	Number	Mean Age	Male	Female	Anterior Mandible	Posterior Mandible	Anterior Maxilla	Posterior Maxilla
DC	Non-inflammatory DC	16	28	22	10	2	25	2	3
	DC with secondary inflammation	16							
OKC	Non-inflammatory OKC	16	32	18	14	2	23	2	5
	OKC with secondary inflammation	16							
DF	Non-inflammatory DF	8	16	8	8	1	11	3	1
	Thickened DF	8							

Post hoc test results for the three markers revealed that the only significant difference in COX2 expression was between DF and DC (p = 0.001). For SOX2 and Nestin, all differences between the groups were significant, except between DF and DC in Nestin expression (p = 0.157). (Table 4)

The results of the Kruskal-Wallis test showed that there were significant differences in the scores between inflammed and non-inflammatory groups in DC and OKC, as well as in the thickened and normal groups of DF for the SOX2 and Nestin markers, unlike COX2 (P-value for COX2, SOX2, and Nestin was calculated as 0.213, 0.002, and 0.000, respectively).

Figure 1 shows the microscopic images with 100x magnification of Nestin, COX2, and SOX2 expression in DC, OKC, and DF.

The highest mean percentage of COX2, SOX2, and Nestin expression was observed in DC, OKC, and DF, respectively (Table 5).

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Table 4- Pairwise comparison of COX2, SOX2, and Nestin expression between study groups

Marker	Comparison	p-value
COX2	DF - DC	0.001
	DF - OKC	0.079
	DC - OKC	0.241
SOX2	DF - DC	0.043
	DF - OKC	0.000
	DC - OKC	0.010
Nestin	DF - DC	0.157
	DF - OKC	0.000
	DC - OKC	0.000

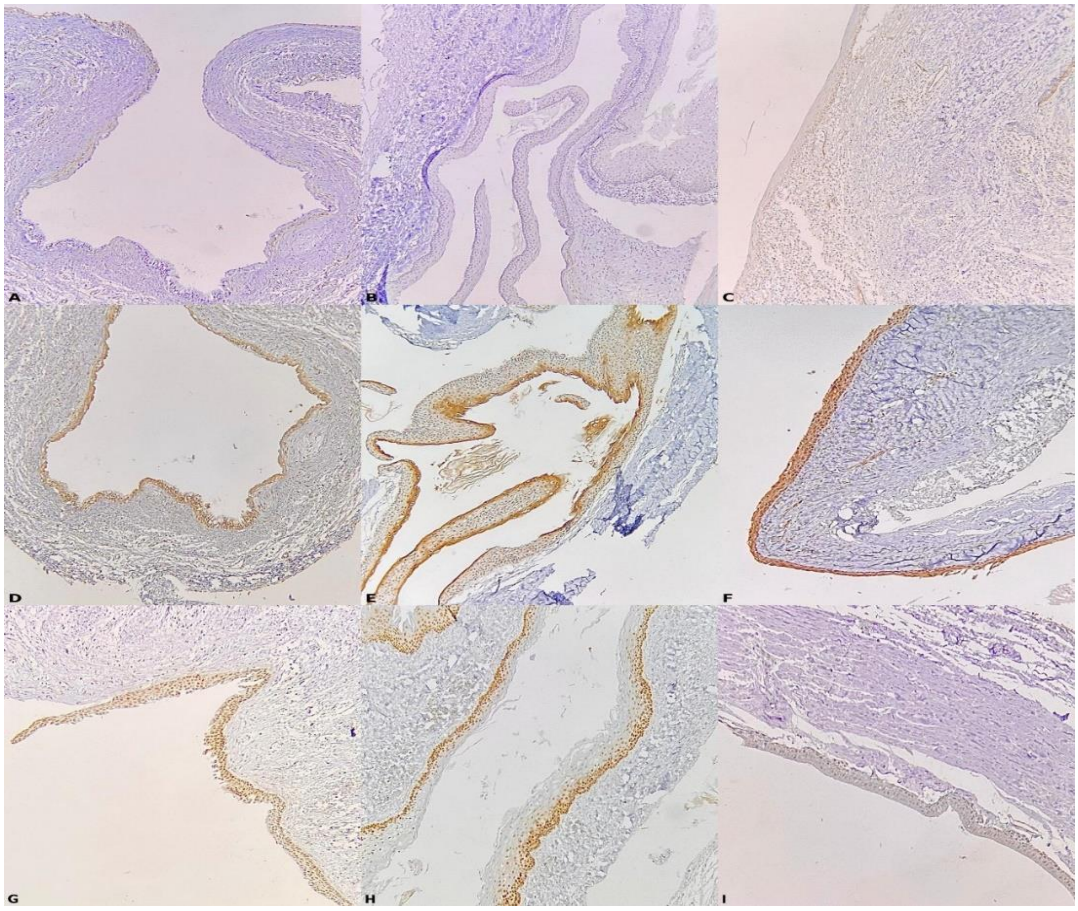

Figure 1: Microscopic images (100x magnification) showing the expression of Nestin, COX2, and SOX2 in DC, OKC, and DF. Images A-C show Nestin expression, D-F show COX2, and G-I show SOX2, each in DC, OKC, and DF, respectively.

Table 5- Comparison of mean percentage and score for COX2, SOX2, and Nestin expression across study groups

Lesion Type	COX2 (Mean % ± SD)	COX2 (Mean Score ± SD)	SOX2 (Mean % ± SD)	SOX2 (Mean Score ± SD)	Nestin (Mean % ± SD)	Nestin (Mean Score ± SD)
DC	88.00 ± 21.00	3.00 ± 0.00	52.00 ± 33.00	2.00 ± 1.00	71.00 ± 29.00	2.00 ± 0.00
Inflamed DC	92.03 ± 4.00	4.00 ± 0.00	58.00 ± 26.06	2.00 ± 0.00	66.00 ± 26.00	2.00 ± 0.00
OKC	90.00 ± 9.00	3.00 ± 0.00	85.00 ± 22.00	3.00 ± 0.00	12.00 ± 5.00	1.06 ± 0.00
Inflamed OKC	84.00 ± 16.00	3.00 ± 0.00	66.00 ± 29.00	3.0000 ± 1.07	17.00 ± 14.00	1.07 ± 0.00
DF	84.00 ± 7.00	3.00 ± 0.00	32.00 ± 27.00	1.00 ± 1.05	88.00 ± 5.00	3.00 ± 0.00
Thickened DF	84.00 ± 3.00	4.00 ± 0.00	24.00 ± 30.00	2.00 ± 1.00	91.00 ± 4.00	3.00 ± 0.00

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Discussion

Despite the significant advancements in understanding OKC and DC, the recurrence rates and tumoral behavior of these lesions pose unresolved questions. A multitude of molecular markers have been investigated to shed light on the aggressive nature of OKC [42], the potential neoplastic transformation in DC [43], and how these characteristics could inform treatment decisions [44]. However, the complexity of their biological behavior remains a challenge in clinical practice. The findings of this study aimed to identify predictive biomarkers for future complications and better treatment plans.

OKC has a strong tendency for aggressive behavior and recurrence. Previous studies have suggested the neoplastic nature of OKC [45]. However, the current consensus based on updated classifications and further research on its biological behavior, views OKC primarily as a cyst rather than a true neoplasm [16]. Molecular research could guide the aggressive surgical treatment approach for this lesion [42]. OKC shows increased cell division and apoptosis and exhibits a unique pattern differentiation compared to DC. Many markers have been studied to explain the differences in the biological behavior of these lesions, which are related to angiogenesis [46], tissue regeneration, and transcription factors [47].

COX2 Marker

COX catalyzes the conversion of arachidonic acid to prostaglandins. Elevated COX-2 expression has been reported in various tumors, particularly those of the esophagus, oral cavity, lungs, and other head and neck sites [29, 48-51]. The underlying mechanism of this upregulation remains unclear. However, it may be related to increased COX2 expression within neoplastic cells [52]. The results of the present study also showed cytoplasmic staining of the cells. Increased COX2 expression has been implicated in dysregulation of cellular processes such as proliferation, adhesion, immune modulation, apoptosis, and angiogenesis, underscoring its role in tumor progression [53]. The current study's findings suggest that DC has the potential for neoplastic transformation and development of other tumors or malignancies. Increased COX2 expression, associated with enhanced angiogenesis and cell proliferation, may explain the higher levels of this marker observed in DC and OKC compared with DF.

Furthermore, several studies have examined molecular markers linked to tumor biology, aiming—like the present study—to understand, explain, and predict molecular processes underlying tumor behavior. Such insights can aid in developing new diagnostic and therapeutic approaches [33, 44].

The results of the present study showed that the mean COX2 expression in OKC and DC was higher compared to DF. These findings imply that COX2 may play a role in tumoral transformations or contribute to more aggressive behavior. Given the similar histopathological features of DC and DF, the significant difference in COX2 expression observed in IHC evaluations may serve as a useful differential marker, though it may not impact the treatment plan.

In this study, COX2 expression in OKC was not significantly higher than in DC, unlike findings from previous research [40, 54]. This discrepancy may be due to limitations in the sample size.

Mendes et al. demonstrated a correlation between COX2 expression levels and the aggressive behavior of OKC, as they observed elevated COX2 expression in these lesions [33, 55]. Similarly, other studies on head and neck tumors are in line with the findings of the present study, reporting increased COX2 expression [50, 56, 57].

COX2 expression is recognized as a key factor in the formation of prostaglandin E2 [58, 59]. Under normal conditions, COX2 expression is minimal but rises in response to pathological stimuli. This elevation increases prostaglandin E2 levels, promoting cell proliferation, angiogenesis, and immune suppression. It has also been shown that interleukin-1 alpha can increase prostaglandin E2 production by upregulating COX2 expression [58], which leads to an increased production of fibroblasts in OKC [60].

Stolina et al. demonstrated that inhibiting COX2 could be effective in reducing lymphocyte infiltration and inhibiting tumor growth [61], proposing COX2 inhibition as a potential strategy for anti-tumor activities. With these explanations to clarify the molecular processes, we compared this marker in odontogenic cysts and tumors. The Sonic Hedgehog (SHH) signaling pathway is recognized as a molecular cascade involved in DC [62] and ameloblastoma [63]. It appears that COX2, through the SHH pathway, leads to the production of P53 and activation of the Ras/Raf/ERK cascade, which in turn feedbacks to further increase COX2 expression [64, 65]. This pathway is a key factor in lesion expansion in bone and resorption of the surrounding hard tissue [65].

COX2 increases both in bone repair processes and pathological conditions such as neoplasms or inflammation [66]. In inflammatory types of OKC and DC, their expression is elevated, which is not related to the tumoral process. However, in non-inflammatory types, increased COX2 expression in DC indicates a higher potential for tumoral behavior.

Driemel et al. found that the expression of COX2 in ameloblastoma was significantly higher compared to OKC. On the other hand, they reported a higher recurrence rate in OKC. Consequently, they concluded that the higher recurrence rate is related to inadequate resection and is likely not influenced by cellular markers [67].

SOX2 Marker

The SOX2 family is derived from the translation of the sex-determining region (SRY). These proteins play significant roles in development, tissue homeostasis, reprogramming, and neoplasms [68]. Studies have shown that SOX2 is

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involved in tumorigenesis and is associated with aggressive behavior and poor prognosis in various cancers, including SCC [69]. In this context, given that human papillomavirus (HPV) infection is a well-established risk factor for oral and head and neck SCC, accumulating evidence suggests that SOX2 may function as a regulator of HPV transcription [70, 71].

In the present study, SOX2 expression was significantly higher in OKC and DC compared to DF, indicating that SOX2 could serve as a marker for neoplastic potential of odontogenic lesions.

Previous studies on SOX2 expression have yielded conflicting results. Some independent studies have shown decreased SOX2 expression in ameloblastoma [41, 68], while Juuri et al. reported increased levels of SOX2 in ameloblastoma [72].

Regarding OKC, there is more consensus results similar to the findings of the present study. Heikinheimo et al. [73] and Banerjee et al. [68] have reported a significant increase in SOX2 expression in OKC compared to the control group. This can be explained by the relatively complete cellular differentiation in the basal and suprabasal layers of the OKC epithelium compared to the ameloblastomas [41]. The expression of SOX2 proportionally increases during the lesion's progression [74]. The increased SOX2 expression observed in the present study may explain the high mitotic index and aggressive nature of OKC, while in the DC, SOX2 was expressed to a lesser extent in the basal layer of the epithelium.

Banerjee et al. in an immunohistochemical analysis of SOX2 on DC, radicular cysts, adenomatoid odontogenic tumors, and ameloblastic carcinomas, demonstrated that in DC, SOX2 was predominantly stained in the basal layer [68].

The recurrence of OKC after surgery is often linked to factors such as satellite cysts, incomplete enucleation, fragile epithelial lining, and the patient's inherent tendency to develop cysts from residual dental lamina [75]. Additionally, the presence of cancer stem cells may also be a contributing factor to recurrence. Based on the results of the present study, targeting these cells with their specific markers could be a significant step toward preventing the recurrence of these lesions.

Nestin Marker

Nestin is an intermediate filament in the cytoskeleton and is recognized as a marker for neural progenitor cells [76]. This protein plays a role in the early development of the central nervous system and the muscular system. Nestin expression has been reported in other tissues and pathological conditions in neural crest derivatives [76] such as the heart [77] and the testes [78]. It has also been observed in reactive astrocytes of the brain and tumors of the central and peripheral nervous systems [79-84].

Nestin expression by odontogenic tumors of mesenchymal and mixed origin appears logical since dental ectomesenchymal tissue is derived from the neural crest [85-87]. However, it is known that Nestin is not typically present in human odontogenic ectomesenchyme throughout life and is only found during brief periods such as odontogenesis and dentin repair [88, 89]. Additionally, odontogenic mesenchymal tissues do not differentiate into neural or muscular tissues. Therefore, immunohistochemical studies have shown varying distribution and intensity in odontogenic tumors [90]. Previous studies have shown that tumors lacking odontogenic ectomesenchymal tissue, such as ameloblastoma and malignant ameloblastoma, do not express Nestin [90]. On the other hand, in mixed odontogenic tumors like ameloblastic fibroma, ameloblastic fibro-odontoma, and ameloblastic fibrosarcoma, intensely Nestin-stained areas are found around the follicular neoplastic odontogenic epithelium [90]. This staining pattern is also observed in odontogenic fibroma. Nestin is typically localized at the interface between the odontogenic epithelium and ectomesenchyme in odontogenic tumors, as confirmed by this study. The highest Nestin expression was found in DF, indicating that its expression pattern varies among odontogenic cysts and tumors and may reflect underlying biological processes. This suggests that DF connective tissue has a fully odontogenic ectomesenchymal origin, whereas the fibrous capsule of OKC lacks this origin, explaining its lower Nestin expression. For the DC, since it originates from the reduced enamel epithelium (REE), the odontogenic ectomesenchymal characteristics are still present in the capsule of the cyst, so similar to the DF, it contains ectomesenchymal cells of neural crest origin, which have the potential to differentiate into other cell types. Moreover, there was no significant difference in Nestin expression between lesions with secondary inflammation and non-inflammed lesions in the present study, indicating that this marker is not involved in inflammatory processes.

The limitations during staining (pH and appropriate concentration) were due to a lack of scientific documentation, which we overcame through trial and error and the assistance of an experienced expert. Moreover, it is recommended that future studies be conducted with larger sample sizes using a multi-center approach, utilizing other ectomesenchymal and tumoral transition markers, as well as molecular analyses such as RT-PCR.

Conclusion

It can be concluded from the findings of the present study that the markers COX2, SOX2, and Nestin can assist in diagnosing inflammatory types. It is also evident that COX2 may be useful in explaining OKC's aggressive behavior. Nestin may serve as a potential marker for identifying ectomesenchymal stem cells, although it does not appear to play a role in the process of cyst development. The

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expression of COX2 and SOX2 in DC suggests the potential for tumoral behavior. The presence of Nestin in OKC suggests that the connective tissue part of the cyst wall is not associated with dental ectomesenchyme. Examining the expression of molecular markers in IHC evaluations can be important for understanding the aggressive nature of lesions and thus may lead to changes in treatment plans to reduce future complications.

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Data Availability Statement: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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