Original Article

Immunohistochemical expression of SOX2 in OKC and ameloblastoma: A comparative study

Treville Pereira, Subraj J. Shetty, Vishal Punjabi, Rutuja G. Vidhale, Swati S. Gotmare, Pooja Kamath

Department of Oral and Maxillofacial Pathology, D.Y. Patil University, School of Dentistry, Navi Mumbai, Maharashtra, India

Abstract

Introduction: Odontogenic, non-inflammatory maxillofacial cysts and tumours vary greatly in their ability to grow and cause local tissue destruction. Despite their common embryologic origin, the biologic mechanisms responsible for this diverse array of clinical behaviour are largely unknown. Unfortunately, even with accurate tissue diagnosis and appropriate surgical management, these tumours have relatively high recurrence rates. While this may be related to surgical technique, it may also be due to intrinsic tumour biology. SOX2 is differentially expressed in odontogenic cysts and tumours, which has an impact over patient prognosis. This could be related to their diverse cells of origin or stages of histogenesis. SOX2 is expressed in OKC and ameloblastoma, and in this study, we look forward to find altered levels and intensity of SOX2 in the above-mentioned lesions.

Aim and Objectives:

- To profile the expression of SOX2 in odontogenic keratocyst (OKC) and ameloblastoma
- To compare the intensity of these lesions, analyse their intrinsic feature and predict their recurrence

Material and Methods: Histopathologically diagnosed cases of OKC and ameloblastoma will be selected (n = 40). Paraffin-embedded, formalin-fixed sections of these lesions will be stained for SOX2 marker using a standard immunohistochemical technique. Positive control will be taken as oral squamous cell carcinoma and negative control will be taken as normal oral mucosa.

Results: A comparison between the stained cell types in odontogenic keratocyst and ameloblastoma revealed statistically significant differences. The immunoreactivity scores of SOX2 were analysed in both groups. The results indicated that 45% of OKC cases exhibited strongly positive reactivity, while 65% of ameloblastoma cases were negative. Statistical analysis demonstrated highly significant differences in the frequency of SOX2 expression between the two groups, with a higher frequency of negative expression in ameloblastoma.

Conclusion: Stem cell markers have been observed in these lesions, suggesting the acquisition of stem-like properties by tumour cells, which can affect patient prognosis. Specifically, the marker SOX2 shows differential expression in odontogenic cysts and tumours. High expression of SOX2 in OKC indicates the presence of stem cells with significant self-renewal and proliferative properties, potentially signifying neoplastic behaviour. In contrast, weak or absent expression of SOX2 in ameloblastoma suggests different molecular pathways involved in its neoplastic behaviour.

Keywords: Ameloblastoma, odontogenic keratocyst, sox2

Address for correspondence: Dr. Treville Pereira, Department of Oral and Maxillofacial Pathology and Microbiology, D.Y. Patil Deemed University, School of Dentistry, Sector 7, Navi Mumbai - 400 706, Maharashtra, India.
E-mail: trevillepereira@gmail.com

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INTRODUCTION

Odontogenic cysts and tumours are derived from epithelial, ectomesenchymal or both the elements of the tooth-forming apparatus. The jaws are host to a wide variety of cysts and tumours because a large part of the tissue is involved in tooth formation. These generally show slow, expansive growth and in some cases are associated with marked bone destruction and recurrence.[1,2]

Ameloblastoma and odontogenic keratocyst (OKC) are among the most common odontogenic lesions. They have similar sites of presentation in the mandibular molar region and variable recurrence rates, with that of OKC being somewhat lower than that of ameloblastoma. The peak age of ameloblastoma is in the fourth and fifth decades and that of OKC is in the second and third decades. Ameloblastoma and OKC are believed to arise from dental epithelial cells, although the exact cell of origin for these tumours is unknown.[3] The development and progression of these tumours involve a series of genetic and molecular alterations. Moreover, these tumours are aggressive in nature and tend to recur, the exact mechanism of which still remains unclear. This may be attributed to the presence of stem cell population called the cancer stem cells (CSCs).[4] These CSCs are defined as a small subpopulation of cancer cells that constitute a pool of self-sustaining cells with the exclusive ability to cause the heterogeneous lineages of cancer cells that comprise the tumour.[5] These cells have three main characteristics: potent tumour initiation, self-renewal *in vivo* and differentiation capacity allowing them to give rise to a heterogeneous progeny, which represents a phenocopy of the original tumour. They arise from normal stem cells or progenitor cells, which undergo further genetic alterations, become dedifferentiated and acquire CSC features. They may originate from the fusion of a hematopoietic stem cell with a mutated epithelial somatic cell or from dedifferentiation of a mature cell.[6] OCT4 and SOX2 are the two major transcription factors, which are required to maintain the pluripotent and self-renewal capacity. Embryonic stem cell (ESC) markers such as OCT4 and SOX2 are capable of identifying these stem cells expressed during the early stages of tooth development (dental papilla and dental lamina cells).[7,8]

Sox2 belongs to a large family of SRY-related HMG box transcription factors that are important during development and cellular differentiation. This gene is located on chromosome 3p26.3-q27 and encodes a protein of 317 amino acids comprising of three main domains: high mobility group (HMG) domain at the N-terminus, dimerization (DIM) domain at the centre and transactivation (TAD) domain at the C-terminus 1.[9] Sonic hedgehog (SHH) is a secreted signalling protein that plays many important roles in cerebellar development and CNS development [Figure 1].

Odontogenic cysts and tumours are a diverse group of lesions originating from the tissue remnants of the

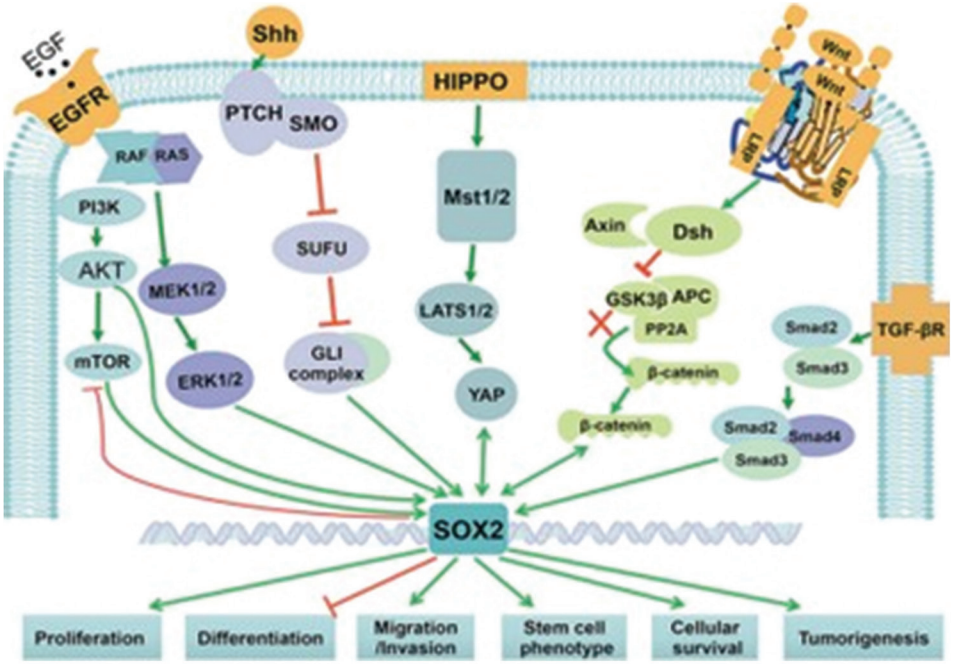


Figure 1: SOX2 cross-talks with a variety of signalling pathways that regulate proliferation, survival and tumorigenesis

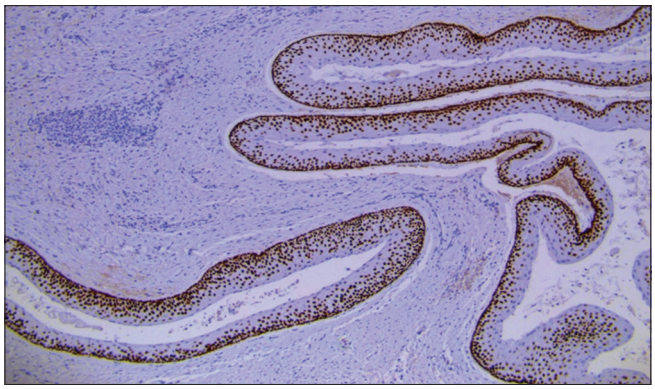


Figure 2: IHC expression of SOX2 in odontogenic keratocyst (100x)

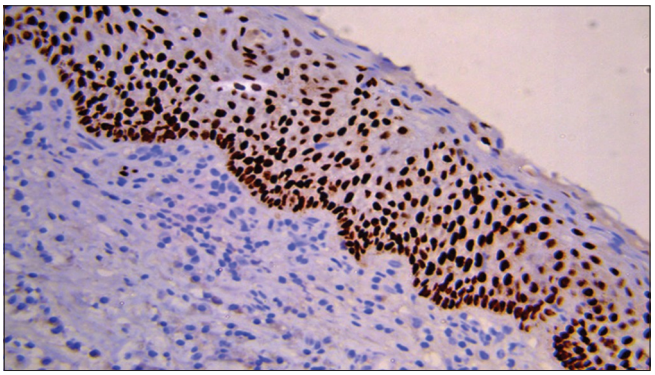


Figure 3: IHC expression of SOX2 in odontogenic keratocyst (400x)

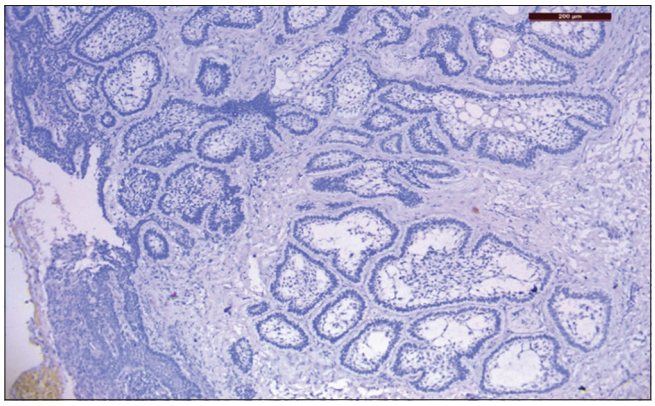


Figure 4: IHC expression of SOX2 in ameloblastoma (100x)

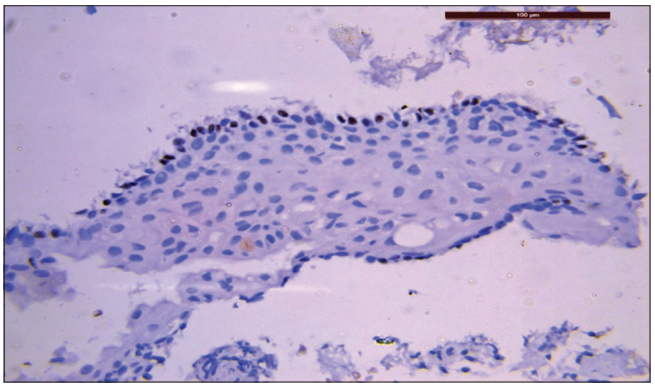


Figure 5: IHC expression of SOX2 in ameloblastoma (400x)

tooth forming apparatus or due to inflammation. The pathogenesis of different types of odontogenic cysts and tumours is far from understood. Among various odontogenic cyst and tumours, OKC and ameloblastoma are considered to be highly aggressive.[10] Various studies were conducted in pre-malignant and malignant lesions of the oral cavity using SOX2 marker; however, very few studies have explained their role in odontogenic cysts and tumours.[11-16]

AIM AND OBJECTIVES

To predict the recurrence of odontogenic keratocyst and ameloblastoma using SOX2 expression

- To profile the expression of SOX2 in odontogenic keratocyst and ameloblastoma
- To comparatively analyse the intensity and intrinsic features of SOX2 in the most aggressive odontogenic cyst (odontogenic keratocyst) and tumour (ameloblastoma)

MATERIALS AND METHODS

The present study entitled was conducted in the Department of Oral Pathology and Microbiology at the institute hospital. The study was approved by the Institutional Ethical Committee. The study consisted of 20 cases of each histopathologically diagnosed OKC and ameloblastoma. In total, 40 cases were included in this study, inclusion criteria were taken as histopathologically diagnosed cases of OKC and ameloblastoma, and exclusion criteria were other odontogenic cysts and tumours. Formalin-fixed paraffin-embedded tissue sections of OKC and ameloblastoma were obtained from the Department of Oral pathology and Microbiology. The sections were immunostained with primary antibody SOX2 for the evaluation of expression of SOX2. The semi-quantitative analysis of SOX2-positive cells was evaluated; nuclear immunoreactivity was considered and was accordingly scored. The immunohistochemical evaluation was performed and statistically analysed using criteria described by Phattarataratip *et al*.[10] The positive immunoreactivity localized at the nucleus was evaluated. All data were entered into a computer by a coding system, proofed for entry errors. Data obtained were compiled on a MS Office Excel Sheet (v 2019, Microsoft Redmond Campus, Redmond, Washington, United States). Data were subjected to statistical analysis using the Statistical Package for Social Sciences (SPSS v 26.0, IBM). Descriptive statistics like frequencies and percentage for categorical data, mean and SD for numerical data have been depicted. Intergroup comparison (two groups) was done using *t* test,

and comparison of frequencies of categories of variables with groups was done using the Chi-square test. For all the statistical tests, $P < 0.05$ was considered to be statistically significant, keeping α error at 5% and β error at 20%, thus giving a power to the study as 80%.

Results and observations

In this study, we investigated SOX2 protein immunohistochemical expression in odontogenic keratocyst and ameloblastoma and their comparison. The study comprised of two groups, 20 histopathologically diagnosed cases of odontogenic keratocyst and ameloblastoma. Group 1, odontogenic keratocyst, and group 2, ameloblastoma, were distributed according to age, gender and anatomical site.

Age

The mean age distribution for group 1 (Odontogenic keratocyst) was 32.10 with the standard deviation of 10.755, and for group 2 (Ameloblastoma), the mean age was 35.25 with standard deviation of 15.430.

Gender

In group 1 (odontogenic keratocyst), out of 20 cases, nine were females and 11 were males.

In group 2 (Ameloblastoma) as well, out of 20 cases, nine were females and 11 were males. So, in total, this study comprised of 55% males and 45% females. There was a statistically non-significant difference seen for the frequencies between the groups ($P > 0.05$).

Anatomical site

In group 1 (odontogenic keratocyst), out of 20 cases, 16 cases were in mandibular posterior, 2 in maxillary anterior and 1 each in maxillary posterior and mandibular anterior region, whereas, in group 2 (Ameloblastoma), out of 20 cases, 16 cases were in mandibular posterior and 4 in mandibular anterior region. There was a statistically non-significant difference seen for the frequencies between the groups ($P > 0.05$).

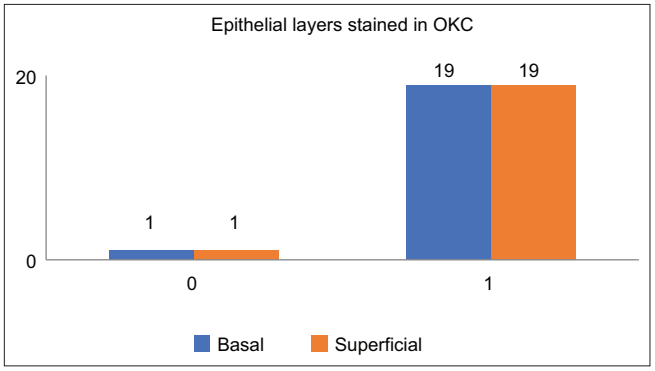
Expression of SOX2 protein OKC and ameloblastoma

The expression of SOX2 protein was assessed using immunohistochemical staining, with brown colour indicating positive expression in the nucleus of epithelial cells. The immunoreactivity score was determined based on the percentage and staining intensity of expression in both groups.

In odontogenic keratocyst (OKC), SOX2 immunostaining was predominantly observed in the nucleus of basal and suprabasal cells of the epithelium lining. A stronger expression of SOX2 was noted in the basal layer of OKC. Among the 20 OKC cases, 19 exhibited positive expression in both basal and superficial layers of the epithelium, while 1 case showed no positive expression at all [Graph 1]. [Figures 2 and 3] On the other hand, ameloblastoma cases displayed relatively lower levels of SOX2 expression. SOX2 was expressed in ameloblast-like cells in all cases, while stellate reticulum-like cells did not show SOX2 expression in any of the cases [Graph 2]. [Figures 4 and 5]

A comparison between the stained cell types in odontogenic keratocyst (group 1) and ameloblastoma (group 2) revealed statistically significant differences. The cells showing positivity in the basal and superficial layers were scored as 1 for positive staining and 0 for no staining. Higher values were observed in group 1, indicating more positive staining compared to group 2 [Table 1].

The immunoreactivity scores of SOX2 were analysed in both groups. In odontogenic keratocyst (group 1), out of 20 cases, 9 showed strongly positive reactivity, 7 showed moderate reactivity, and 2 each showed mild and negative reactivity. In ameloblastoma (group 2), 13 cases were negative, 5 showed mild reactivity, and 2 showed moderate reactivity, with no cases showing strongly positive reactivity [Tables 2 and 3]. These results indicated that 45%

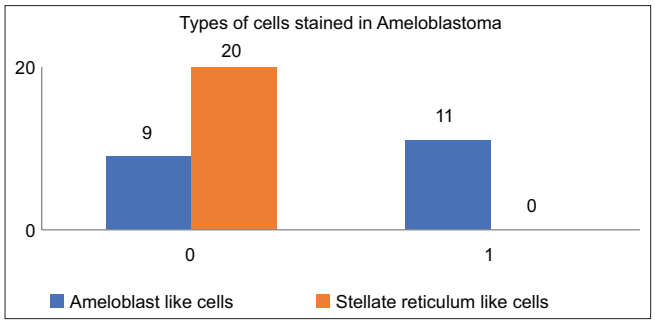


Graph 1: Profile distribution of SOX2 positive cells in distinctive cells types of OKC depending upon their staining intensity (0-No positivity; 1-positive)

Table 1: Correlation of epithelial layers stained in group 1 (odontogenic keratocyst) and group 2 (ameloblastoma) using *t* test

	Group	N	Mean	Std. Deviation	Std. Error Mean	T value	p value of t test
Epithelial layers stained- Basal	1	20	.85	.366	.082	2.135	.039*
	2	20	.55	.510	.114		
Epithelial layers stained- Superficial	1	20	.95	.224	.050	19.000	.000**
	2	20	.00	.000	.000		

*=statistically significant difference ($P<0.05$). **=statistically highly significant difference ($P<0.01$)



Graph 2: Profile distribution of SOX2-positive cells in distinctive cells types of ameloblastoma depending upon their staining intensity (0-No positivity; 1-positive)

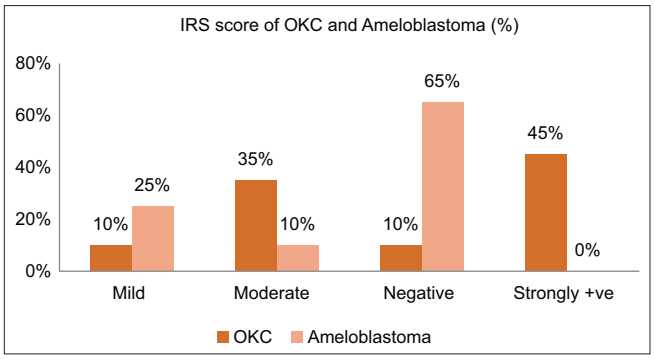
Table 2: Immunoreactivity (IRS) score of group 1 (odontogenic keratocyst) and group 2 (ameloblastoma)

Immunoreactivity score*Groups			
	Group		
	1	2	Total
Mild	2	5	7
Moderate	7	2	9
Negative	2	13	15
Strongly +ve	9	0	9
Total	20	20	40

Table 3: Correlation of mean percentage of IRS score in group 1 (odontogenic keratocyst) and group 2 (ameloblastoma)

Percentage analysis of IRS score*Groups		
	Group 1	Group 2
Mild	10%	25%
Moderate	35%	10%
Negative	10%	65%
Strongly +ve	45%	0%
Total	100%	100%

of OKC cases exhibited strongly positive reactivity, while 65% of ameloblastoma cases were negative [Graph 3].



Graph 3: Correlation of mean percentage of IRS score in group 1 (OKC) and group 2 (ameloblastoma)

Statistical analysis demonstrated highly significant differences in the frequency of SOX2 expression between the two groups, with a higher frequency of negative expression in ameloblastoma (group 2) [Table 4].

DISCUSSION

The molecular basis of odontogenic competence in early jaw epithelium and later in the condensed dental mesenchyme remains elusive. As all the genes that are known to regulate tooth development are also expressed in other developing organs, it seems that there is no single tooth specific gene that defines the odontogenic tissues. Currently, only a few genes such as Sonic hedgehog (Shh) and the transcription factor Pitx2 are known to be restricted to the dental lamina.[17] Reciprocal signalling between epithelium and ectomesenchyme guides the process of tooth embryonic development, which is fully dependent on Wnt, BMP, FGF, Shh and Eda signals. The pathogenesis of odontogenic tumours is associated with alterations in components of signalling pathways.[18]

Cysts and tumours derived from the odontogenic tissues constitute an unusually diverse group of lesions. This diversity reflects the complex development of the dental structures, since all these lesions originate through some alteration from the normal pattern of odontogenesis. Some lesions included in this category may in fact not represent neoplasia at all, but are only minor alterations in the normal process of tooth development. Lesions such as cysts are also tumours only in the broadest sense of the word and do not represent true neoplasms.[19] Two such aggressive and most commonly recurring odontogenic cysts and tumours are odontogenic keratocyst and ameloblastoma.[20] The molecular pathogenesis and the mechanisms involved in their aggressive behaviour are mostly unknown. A probable explanation for these could be the presence of stem cells, hypothesizing that odontogenic lesions contain

Table 4: Correlation of immunoreactivity score between the two study groups using the chi-square test

Chi-Square Tests			
	Value	df	P value
Chi-Square	21.130[a]	3	.000*

**=statistically highly significant difference ($P<0.01$)

a small population of the stem cells, which has three important imbibed properties such as self-renewal, colony formation and pluripotency. Stem cells are unspecialized cells defined as clonogenic cells that have the capacity for self-renewal and the potential to differentiate into one or more mature cellular lineages. They support histogenesis and organogenesis during development, maintaining a balance in the cell turnover process and also have a regenerative capacity in the adult tissues. It is generally a well-agreed fact that the embryo is a potential source of pluripotent progenitor cells, which divides and gives rise to different types of cells, specialized in forming different tissues.[7] There are four important cell-specific factors, which are expressed in the cells with pluripotent capacity, i.e., octamer-binding transcription factor 4 (OCT4), sex-determining region Y (SRY)-box2 (SOX2), NANOG and c-Myc.[7]

During normal odontogenesis, different types of odontogenic epithelium and odontogenic ectomesenchyme variably express SOX2. Its expression is observed in a time-dependent manner in ameloblasts, odontoblasts, dental papilla and dental follicle. The dental lamina of developing human primary molar expresses SOX2, whereas no expression of this protein was detected in Hertwig's epithelial root sheath or epithelial rests of Malassez. The presence of SOX2-positive stem cells in dental lamina indicates the epithelial competence for tooth development and supports the renewal of ameloblasts and other dental epithelial lineages.[10]

To the best of our knowledge, a few studies have described expression of SOX2 in odontogenic cysts and tumours. Also, there are very few studies that have compared the two most aggressive odontogenic cyst and tumours, i.e. OKC and ameloblastoma.[10,21-23]

The present study aimed to investigate immunohistochemical expression of SOX2 in the most aggressive cyst and tumours of the oral cavity, i.e. OKC and ameloblastoma and to correlate and compare their intensity and intrinsic features with relation to SOX2.

The present study consisted of two study groups: Group I, 20 histopathologically diagnosed cases of OKC, and Group II, 20 histopathologically diagnosed cases of ameloblastoma. The demographic data obtained from the case history proforma were evaluated and tabulated for age, gender and anatomical site.

The mean age for the OKC group was 32.10 years, and the mean age for the ameloblastoma group was 35.25 years. A male predominance was observed in OKC and ameloblastoma study groups having 55% cases in males and 45% in females. A definite male predilection was seen in this study similar to the findings of Ramachandra *et al.* (2011), Kambalimath *et al.* (2014), Rubini *et al.* (2017)[19,24,25] and differed with Deepthi *et al.* (2016), Rafael *et al.* (2017) and Mehengi *et al.* (2018), which showed a female predilection.[26-28]

In the OKC group, the mandibular posterior region was the most commonly affected site; a few cases were observed in maxillary and mandibular anterior region and maxillary posterior region as well. This finding was in accordance with other studies, Avelar *et al.* (2008), Ramchandra *et al.* (2011), Selvamani *et al.* (2012), Kambalimath *et al.* (2014), Deepthi *et al.* (2016) and Nalabou *et al.* (2017)[24,27,29-32]

Similarly, in the ameloblastoma group, the most commonly affected site was the mandibular posterior region with a few cases in the mandibular anterior region and no case was observed in the maxillary jaw. Thus, the most frequent site reported was posterior mandible, which in consistent with many studies conducted by Avelar *et al.* (2008), Varkhade *et al.* (2011), Taghavi *et al.* (2013), Deepthi *et al.* (2016) and Ahire *et al.* (2018).[27,30,33-35]

Th present study showed a greater expression of SOX2 in OKC than ameloblastoma with noticeable staining in all the cell layers of cystic lining. There was a highly statistically significant difference observed between the two study groups. The immunohistochemical expression of SOX2 in our study group was found in the nucleus. This finding is in accordance with studies carried out by Juuri *et al.* (2013), Behura *et al.* (2017), Silva *et al.* (2020) and Phattarataratip *et al.* (2021) in which nuclear expression of SOX2 was noted.[10,21-23]

A study conducted by Juuri *et al.* (2013) using SOX2 marker in ameloblastoma concluded a positive SOX2 expression in epithelial cells of follicular and plexiform ameloblastoma, which differed from the results of the present study.[22]

Lei *et al.* (2014) evaluated the role of SOX2 in ameloblastoma, atypical ameloblastoma (AA) and ameloblastic

carcinoma (AC). They found SOX 2 staining to be essentially negative in most of the ameloblastoma and AA cases, while a significantly higher immunohistochemistry (IHC) score was seen in AC. They concluded that SOX2 could be used as a marker for AC as well as for high-grade transformation in ameloblastic neoplasms.[36]

Kamath*et al*. (2016) performed IHC in follicular tissue, radicular cyst, dentigerous cyst, odontogenic keratocyst, ameloblastoma, adenomatoid odontogenic tumour and ameloblastic carcinoma. They found that negative expression of both SOX2 and OCT4 was observed in ameloblastoma, whereas odontogenic keratocyst showed a positive SOX2 expression and a negative OCT4 expression, which was in accordance with the present study.[7]

Another study conducted by Behura *et al*. (2017), the expression of cancer stem cell markers OCT4 and SOX2 was evaluated in ameloblastoma and odontogenic keratocyst. They observed no OCT4 positivity in ameloblastoma or OKC. Also, ameloblastoma showed SOX2 negativity, while high SOX2 expression was found in OKC, which was in sync with the present study.[21]

Immunohistochemical analysis performed by Silva *et al*. (2020) to evaluate SOX2 and BCL-2 expression in OKC and ameloblastoma showed SOX2 and BCL-2 expression was observed in all specimens of OKC in the full thickness of the epithelium lining. Also, SOX2 immunostaining was higher in OKC, in comparison with ameloblastoma samples.[23]

Phattarataratip *et al*. (2021) analysed the expression and significance of SOX2 and OCT4 in various types of odontogenic cysts and tumours including odontogenic keratocyst and ameloblastoma. Their study showed most OKCs (86.7%) expressed SOX2 in more than 50% of epithelial cells; however, SOX2 expression was undetectable or limited to the ameloblastoma cases. Similar results were observed in the present study.[10]

CONCLUSION

Cysts and tumours derived from odontogenic tissues are a diverse group of lesions. Among them, odontogenic keratocyst (OKC) and ameloblastoma are known to be aggressive and frequently recurring. Stem cell markers have been observed in these lesions, suggesting the acquisition of stem-like properties by tumour cells, which can affect patient prognosis. Specifically, the marker SOX2 shows differential expression in odontogenic cysts and tumours. High expression of SOX2 in OKC indicates the presence of stem cells with significant self-renewal and proliferative properties, potentially signifying neoplastic behaviour. In contrast, weak or absent expression of SOX2 in ameloblastoma suggests different molecular pathways involved in its neoplastic behaviour.

The expression of SOX2 in OKC may be linked to the biological behaviour of the lesion and its potential influence on the Hh signalling pathway. Recurrence of OKCs after surgical treatment can be attributed to various factors, including the presence of satellite cysts, incomplete removal during surgery, difficulties in enucleation of thin and fragile linings, and the intrinsic tendency of patients to develop cysts. It is hypothesized that the presence of a stem cell population contributes to OKC recurrence due to their self-renewal and pluripotency properties. In summary, odontogenic cysts and tumours, particularly OKC and ameloblastoma, exhibit diverse characteristics. The expression of SOX2 serves as a reliable marker for identifying stem cell populations in OKC, indicating its potential neoplastic behaviour. Recurrence of OKCs may be influenced by the presence of stem cells, which possess self-renewal and pluripotency abilities. Understanding these factors is crucial for better management and prognosis of odontogenic lesions.

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Conflicts of interest
There are no conflicts of interest.

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