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Research Article

PROSPECTIVE SIGNIFICANCE OF CYCLOOXYGENASE-2 IN KERATOCYSTIC ODONTGENIC TUMOR: AN IMMUNOHISTOCHEMICAL STUDY DIFFERENTIATING THE TUMORAL AND THE CYSTIC NATURE OF ODONTOGENIC LESIONS

Neha Bhomia[1]., Devesh Bhomia[2] and Nida Fahmi[3]

[1,3]Department of Oral Pathology & Microbiology, Jaipur Dental College, Jaipur
[2]SMS Medical College & attached Group of Hospitals, Jaipur

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A B S T R A C T

Background: Keratocystic odontogenic tumor (KCOT) is a benign intraosseous neoplasm with locally invasive behaviour and a tendency to recur. Dentigerous cyst (DC) is one of the most common type of the developmental odontogenic cysts, having the capability of becoming an aggressive lesion. Both can cause involvement of adjacent soft tissues, infiltration and destruction of the bone. Although the exact etiology and pathogenesis of these two odontogenic lesions remain unclear, recent studies have identified several molecular changes that are attributed to their development and progression of the lesions. Cyclooxygenase-2 (COX-2) is an enzyme involved in prostaglandin synthesis that modulates the formation of neoplasm. With the use of COX-2 our study supports the current neoplastic concept of KCOT highlighting its aggressive and recurrent nature and the non-neoplastic and cystic nature of DC.

Materials and Methods: In this study, the expression of COX-2 in 40 specimens (30 KCOT; 20 primary and 10 recurrent, 10 DC) has been analyzed. Sections of colon carcinoma were used as positive controls. Formalin fixed, paraffin-embedded blocks were sectioned and used for Hematoxylin-eosin (H&E) staining and incubated with an anti-COX-2 monoclonal antibody for immunohistochemical (IHC) examination.

Results: Cellular staining pattern for COX-2 was cytoplasmic, seen mainly in the epithelial lining and were semi-quantitatively evaluated as negative (-), mild (+), strong (++). In KCOT, majority of cases demonstrated intense COX-2 immunostaining whereas in the DC it showed negative to mild immunostaining. Shift in color from negative to strong immunostaining in cases of KCOT and DC was attributed to more aggressive and neoplastic nature of the lesion. Thus results of our study demonstrated that COX-2 plays a key role in the network of molecular pathways of the biologic genetic and epigenetic events that lead to the KCOT's aggressive behaviour.

Conclusion: The study explains the difference in the pathophysiology of these two odontogenic lesions; KCOT as a neoplasm and DC as a cystic lesion.

INTRODUCTION

The OKC has been one of the most controversial pathological entities of the maxillofacial region since Philipsen first described it in 1956.[1] Because of its clinico pathological features, the revised classification of Head & Neck tumors, published in 2005 by the WHO has reclassified OKC as a benign intraosseous neoplasm thus recommending the term KCOT.[2] KCOT is defined as "a benign uni or multicystic, intraosseous tumour of odontogenic origin, with a characteristic lining of parakeratinized stratified squamous epithelium and potential for aggressive, infiltrative behaviour".[2]

Corresponding author:* **Neha Bhomia
Department of Oral Pathology & Microbiology, Jaipur Dental College, Jaipur

Malignant transformation into squamous cell carcinoma, although rare has been reported.[3-8] Reported recurrences range from 0.0 % to 100%.[9]

Rajendran & Sivapathasundharam[10] in 2006 stated that DC is one of the most common type of developmental odontogenic cyst having the capability of becoming an aggressive lesion. It is usually associated with the crowns of an unerupted permanent teeth, most frequently associated with impacted mandibular third molars. Although the exact etiology and pathogenesis of these non neoplastic cystic lesions remain unclear, recent studies have identified several molecular changes that are attributed to their development and progression.[11]

COX is a key regulatory enzyme in the conversion of arachidonic acid, a 20-carbon polyunsaturated fatty acid, to prostaglandins (PGs).[12] The COX enzymes have two catalytic activities:[12,13] It catalyzes the addition of molecular oxygen to arachidonic acid and forms an unstable cyclic endoperoxide hydroperoxide: PGG_2. The peroxidase function rapidly reduces PGG_2 to PGH_2, which is converted to one of several structurally related prostanoids, including PGE_2, PGD_2, $PGF_{2\alpha}$, PGI_2 and thromboxane A2 (TXA2), in reactions catalyzed by distinct, specific synthases. There are two known isoforms of COX. COX-1 is constitutively expressed in many tissues and mediates the synthesis of PGs required for normal physiological function. COX-2 is an enzyme that is not found in normal conditions, but which is induced by a variety of physiopathological conditions affecting the tissues, such as growth factors, inflammatory stimuli, oncogenes, carcinogens, tumor promoting phorbol esters and viral transformation.[12-15]Although COX-2 has rarely been used to assess the biologic activity of the KCOT and DC, the current knowledge of overall role known to be played by COX-2 in tumorigenesis suggest that it may be an important marker involved in the pathophysiology of these two odontogenic lesions.

MATERIAL AND METHODS

A retrospective case control study was conducted in the Department of Oral Pathology and Microbiology, Jaipur Dental College, Jaipur. Archival samples of 40 paraffin embedded blocks which included 30 samples of KCOT (20 primary and 10 recurrent) and 10 samples of DC were retrieved from the Department of Oral Pathology and Microbiology, Jaipur Dental College, Jaipur. The diagnosis of the samples of KCOT and DC were confirmed based on WHO criteria. (Table-1)

Table 1 WHO criteria for typing KCOT & DC

S.no	Entity	Who criteria
1.	Primary KCOT	The histologic features are characterized by the presence of a corrugated thin band like parakeratinized stratified squamous epithelium, with a prominent basal layer composed of either columnar or cuboidal cells.
2.	Recurrent KCOT	Recurrent KCOT is defined as KCOT arising at the same location of the primary KCOT after a period of atleast three months. Histopathological features are same as that of primary KCOT.
3.	DC	Uniform thin non keratinized stratified squamous epithelium of 2-3 layer in thickness without rete pegs, lining epithelium similar to reduced enamel epithelium. Non inflamed connective tissue capsule.

Clinical, radiological and histopathological parameters were recorded from the OPD files obtained from the Dept of Oral & Maxillofacial Surgery of Jaipur Dental College, Jaipur, Dept of General Surgery of SMS Medical College, Jaipur and Dept of Oral Pathology and Microbiology of Jaipur Dental College, Jaipur.

One section of 5ụm thickness was cut from each selected paraffin-embedded tissue blocks on normal slides using rotary microtome for H & E staining. Two sections of 0.3 µm thickness were cut from each blocks on poly-L-lysine slides for IHC staining. Briefly, 5 um sections were de-waxed in xylene and hydrated with graded ethanol. For IHC staining, as pre-treatment, microwave-based antigen retrieval was performed. Sections were afterward incubated with a pre-diluted primary rabbit polyclonal anti-COX-2 antibody. (SP-21) (Biogenex CA, USA). Immunoreactions were visualized with diaminobenzidine (DAB) chromogen, and the sections were counterstained with Meyer's hematoxylin and mounted in DPX. Detection of the COX-2 antibody was performed with the IHC kit (Biogenex). The histological section of colon carcinoma was used as a positive control for COX-2. (Fig 1)

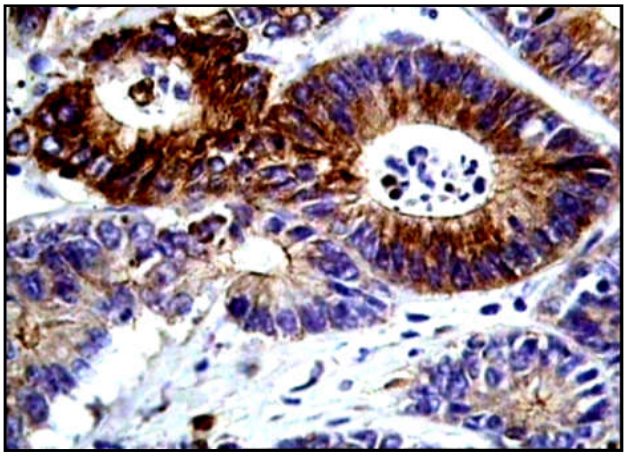


Fig 1 COX-2 expression in positive control (colon carcinoma).

Negative controls were achieved by substituting the primary specific antibodies with the negative control. The intensity of immunoreactive cells was determined using conventional microscopy. Staining intensity was observed at 40x and were graded into three groups: (Table-2) (Fig 2,3,4,5,6,7)

Table 2 IHC COX-2 staining intensity

S.NO	PARAMTERS	OBSERVATIONS
1.	"-" Negative	No staining, when there was no detectable staining of the epithelium or when the staining was somewhat questionable
2.	"+" Mild	Mild staining, when the intensity of the staining was mild in all the epithelium or strong but with an heterogeneous or focal pattern in <50% of the epithelial cells
3.	"++" Strong	Strong staining, when there was a strong and homogeneous staining of more than 50% of the epithelial lining

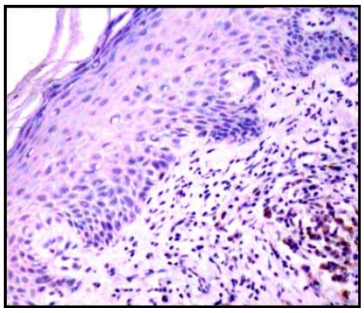


Fig 2 KCOT showing negative COX-2 expression

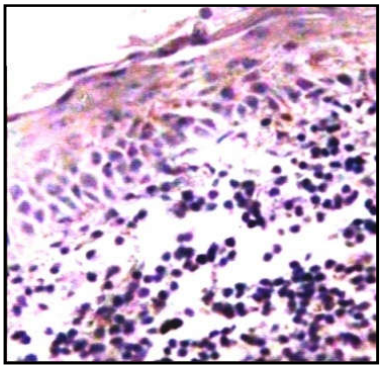


Fig 3 KCOT showing mild COX-2 expression

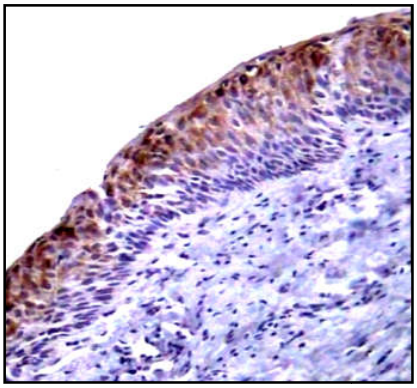


Fig 4 KCOT showing strong COX-2 expression

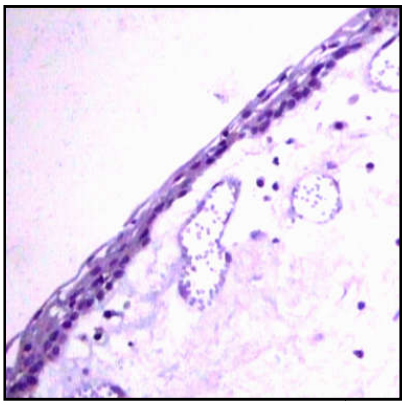


Fig 5 DC showing negative COX-2 expression

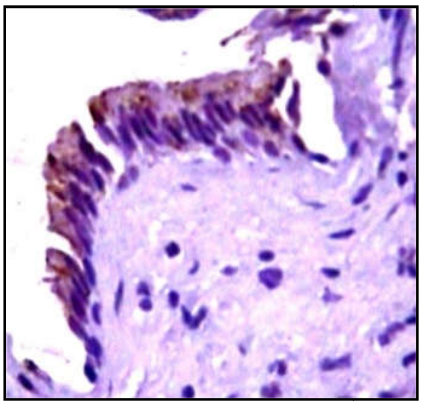


Fig 6 DC showing mild COX-2 expression

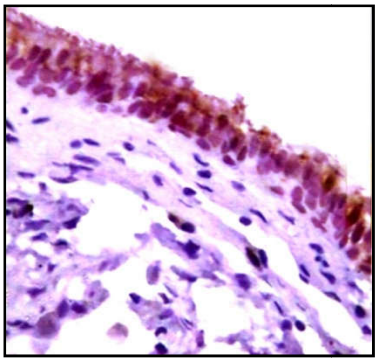


Fig 7 DC showing strong COX-2 expression

Statistical analysis

To eliminate inter-observer variability three observers carried out all these observations which were then subjected to inter observer variability statistical analysis. (Table 3) Spearman correlation analysis was also performed to check the existence of correlation between the variables. pValue: Correlation is significant at the 0.05 level. (<0.05= significant, >0.05= non significant)

Table 3 IHC COX-2 staining intensity: Results of three observers

Subject		IHC COX-2 Staining Intensity			
		Negative	Mild	Strong	Total
Primary KCOT	Count	16	17	27	60
	% within subject	26.6%	28.3%	45%	100.0%
	% within COX-2 staining	64.0%	73.9%	64.2%	66.6%
Recurrent KCOT	Count	9	6	15	30
	% within subject	30%	20%	50.0%	100.0%
	% within COX-2 staining	36%	26.0%	35.7%	33.3%
Total	Count	25	23	42	90
	% within subject	27.7%	25.5%	46.6%	100.0%
	% within COX-2 staining	100.0%	100.0%	100.0%	100.0%
DC	% within COX-2 staining	100.0%	100.0%	100.0%	100.0%
	Count	12	15	3	30
	% within subject	40%	50%	10%	100%

OBSERVATIONS AND RESULTS

In KCOT cases, the male: female ratio was 4:1, with 24 men (80%) and 6 (20%) women. They were found to be more frequent in the second and third decades, overall ranging in age from 10 to 55 years, with a mean age of 31 years. The specimens comprised 20 (66.66%) primary KCOTs and 10 (33.33%) recurrences. Tumors were predominantly located in the angle / ramus of the mandible (66.66%). In DC cases, the male: female ratio was 9:1 with 9 men (90%) and 1 woman (10%). They were more frequent in the second and third decades, overall ranging in age from 10 to 50 years, with a mean age of 23 years. DCs were predominantly located in the angle / ramus of the mandible (50%).

Immunohistochemical analysis: The total results of the COX-2 staining intensity done by the three observers were subjected to inter observer variability statistical analysis. Since there was no statistical difference between the three observations so further evaluation was done with respect to the results of observer 1. Using reliability procedure, estimation of intra-class correlation coefficients (ICCs) was done. As intra-class correlation for all pairs were more than 0.9, it shows statistically all three observations were same.

Table 4 Correlation between variables according to Spearman analysis

Parameters	Correlations	COX-2 staining	Age	Sex	Site
Spearman's RHO					
COX-2 staining	Correlation coefficient	1.000	-0.294	-0.165	0.034
	p Value	.	0.114	0.383	0.858
	N	30	30	30	30
AGE	Correlation coefficient	-0.294	1.000	0.048	-0.436
	p Value	0.114	.	0.800	**0.016**
	N	30	30	30	30
SEX	Correlation coefficient	-0.165	0.048	1.000	0.196
	p Value	0.383	0.800	.	0.300
	N	30	30	30	30
SITE	Correlation coefficient	0.034	-0.436	0.196	1.000
	p Value	0.858	0.016	0.300	.
	N	30	30	30	30

Further the results of the readings of the three observers were subjected to Pearson Ch. Square statistical analysis test which showed a highly significant p value: <0.0001. All the values obtained were further subjected to Spearman correlation statistical analysis to check the existence of correlation between the variables. (Table 4) Results showed that the relation between COX-2 expression and age (p value: 0.114), gender (p value: 0.383) and site (p value: 0.858) was non-significant. However the relation between age and site (p value: 0.016) was significant. Further the relationship of COX-2 immunostaining with primary and recurrent was calculated by the chi-square or χ^2 test, a statistical hypothesis test which showed a non-significant p value: (0.70316683) Further the relationship of COX-2 immunostaining with KCOT and DC was calculated by the chi-square or χ^2 test, a statistical hypothesis test which showed a highly significant p value: (0.00000001)

The majority of KCOT cases included in our study showed the strong expression of COX-2 in the cytoplasm of the epithelial cells, while the DC cases showed mild positivity with only a single case with strong expression. Thus the results of our study portrayed the difference of the COX-2 expression in a neoplasm and a cystic lesion. The staining intensity of COX-2 increases with the aggressive potential of the lesion. Therefore with respect to COX-2 expression seen in the epithelial cells of KCOT and DC, the aggressive potential of KCOT can be explained and thus considering it as a neoplasm and DC as a cystic lesion.

DISCUSSION

DC and KCOT are both odontogenic lesions, but they differ in their biological behaviours, aggressiveness and recurrence rates. KCOT is considered to be neoplastic whereas DC is a non neoplastic lesion. Significant differences seen in the molecular level of KCOT and other odontogenic cystic lesions (DC) suggest the difference in the physiopathological behaviour of these lesions. Several studies have found marked differences between the two lesions with regard to their molecular alterations. Different epithelial-related factors have been found to be involved in the biological behaviour of the odontogenic epithelium, such as proliferative potential as supported by the studies done by Thosaporn *et al* (2004)[11], cell-cycle related pathways Kumamoto *et al* (2001)[16], and tumor suppressor genes Barreto *et al* (2002).[17] The literature suggests that COX-2 plays an important role in tumorigenesis may be an important marker in detecting the aggressive nature of the lesions. Crofford (1997)[18] hypothesized that under normal conditions, COX-2 expression is highly restricted; however, COX-2 is dramatically up regulated during pathological conditions.

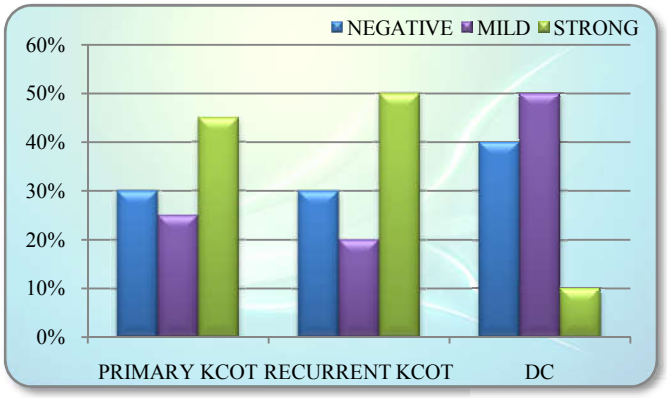
Our IHC data of 30 samples of KCOTs demonstrate positive cytoplasmic COX-2 expression in 21 cases (14 primary and 7 recurrent) in which 7 (5 primary and 2 recurrent) were mild, and 14 (9 primary and 5 recurrent) were strongly positive. The remaining nine cases (6 primary and 3 recurrent) were negative for COX- 2. The overall results showed a distinct overexpression of COX-2 in 21 (70%) of all KCOTs. Numerous studies have been reported which support the strong expression of molecular markers in KCOT thus explaining its aggressive and recurrent potential. Meghji S *et al* (1992)[19] conducted immunohistochemical studies and showed that IL-1a and IL-6 are expressed in the epithelium of KCOTs, suggesting that these cytokines may play a crucial role in KCOTs growth. They stimulate bone resorption by osteoclast-like cell formation and / or activation and the production of prostaglandin, and collagenases. Hence, enhanced synthesis of prostaglandins, is considered as a consequence of upregulation of COX-2, which can increase cell proliferation, promoting angiogenesis and inhibiting immune surveillance. El Murtadi (1996)[20] reported that the proliferating activity of the epithelial cells is strongly related to the aggressiveness of KCOTs. Han *et al* (2002)[21] found that p53-induced COX-2 expression results from p53-mediated activation of the Ras / Raf /MAPK cascade. Furthermore, a p53 downstream target gene – Heparin-Binding Epidermal Growth Factor (HB-EGF) induces COX-2 expression, implying that COX-2 is an ultimate effector in this pathway. IL-1 is known to stimulate the production of PGE2 in KCOTs fibroblasts**.** Moreover, Corcoran CA (2005)[22] found that COX-2 has been found to be upregulated following p53 activation at both the mRNA and the protein levels. In fact, COX-2 negatively affects the transcriptional function of p53 and may mediate such effects by physically interacting with p53**.** Ogata *et al* (2006)[23] found that IL-1a enhanced the expression of COX-2 mRNA and protein, and PGE2 secretion in fibroblasts. He also demonstrated that IL-1a may stimulate COX-2 expression in KCOTs through the NF-β cascade. COX-2 activation has been found to be an early event during carcinogenesis, and its increased expression has been associated with the development of genomic instability. Therefore; the presence of positive staining in the epithelial lining of KCOT might accounts for the presence of altered activated process of COX-2.

On the basis of our current findings and concept, we also observed the COX-2 expression in DCs. Among 10 DC cases; 4 (40%) cases showed negative staining intensity, 5 (50%) showed mild staining intensity and 1 (10%) showed strong staining intensity. The results of our study was in accordance with the study conducted by Mendes *et al* (2011)[24] who evaluated the expression of COX-2 in 10 DC and found a positive expression of COX-2 in 6 out of the 10 DCs. These results substantiate the hypothesis that SHH may in fact be an instigating factor behind developmental cysts, with concomitant aberrant and less expression COX-2 which also shows an amplified physiological process phenomenon. Harris[25] in his research mentioned the role of prostaglandins (PGEs and PGFs as well as PGE2) in cystic growth and bone resorption in DC. According to Horton *et al*[26] growth of the cysts and the bone resorbtion is activated by a variety of humoral agents which includes parathyroid hormone, vitamin D, PGs; lymphokine produced by stimulated B lymphocytes which has been named osteoclast activating factor by Harris.[25] Zhang *et al*. (2010)[27] reported immunoreactivity for SHH, PTCH, SMO, and GLI1 in the epithelial cytoplasm of dentigerous and glandular odontogenic cysts.

In the present study, stratified squamous epithelia of the KCOT and DC showed COX-2 expression normally in the superficial cell layers. However basal cell layer showed very mild or no staining which was supported by the study conducted by Mendes *et al* (2011).[24] Hence the impression is gained that the better the differentiation of the epithelium, the more expression of COX-2 occurred. Though the existing studies also tend to elaborate on the suprabasal pattern of the overexpressed markers, we consider that the somewhat limited thickness of the epithelial lining of the KCOT makes it

difficult to actually analyze molecular marker's expression with regard to its exact location in an objective and reproducible way expression has been associated with the development of genomic instability.

The present study showed that both KCOT and DC harbor COX-2 in their epithelial cells as reflected by the positive immunohistochemical expression but its expression was significantly higher in most of the KCOT samples than in the DC. (Bar diagram 1) This may be due to the intrinsic growth potential of the epithelium and the role of PTCH gene seen in KCOTs.



Bar diagram 1 IHC COX-2 positivity in KCOT and DC cases

However, concomitant less and aberrant expression COX-2 in DC might be due to the malfunctioning pathway of certain molecules (SHH, SMO) hence supporting its non neoplastic and cystic nature as mentioned by Pavelić's hypothesis.[28] Since COX-2 is implicated as a mediator of inflammation and have a possible role in prostanoid signaling in activity-dependent plasticity, it is considered as an ideal marker in detecting the aggressive potential of the lesions irrespective of its primary and recurrent nature.

Our study is in accordance with the study conducted by Mendes *et al* (2011)[24] who found no such association between the expression of COX-2 and any of the clinical features. The fact that no correlation was found between the expression of COX-2 and any of the clinical features only shows that the pathogenic mechanism involved in these tumours is not clinical-related'. In fact, it unveils an intrinsic characteristic of the tumor that bares no association either with its primary or recurrent nature, thus substantiating molecular studies done by Lo Muzio L *et al* (1999)[29], Shear M (2002)[30], Katase N *et al* (2007)[31] which have established an identical mechanism involving the development of both primary and recurrent KCOTs and therefore establishing the neoplastic nature of the KCOT.

CONCLUSION

The study suggests that the expression of COX-2 varies between types of odontogenic lesions; neoplasm and a cystic lesion. The staining intensity of COX-2 increases with the aggressive potential of the lesion. Therefore with respect to the COX-2 expression seen in the epithelial cells of KCOT and DC, the aggressive potential of KCOT and cystic nature of DC can be explained thus considering KCOT as a neoplasm and DC as a cyst**.** Since, COX-2 is implicated as a mediator of inflammation and have a possible role in prostanoid signaling in activity-dependent plasticity, it is thus considered as an ideal marker in detecting the aggressive potential of the lesions irrespective of its primary and recurrent nature.

Acknowledgements

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Declarations

Ethics approval and consent to participate: The archival samples were collected from Department of Oral Pathology & Microbiology, Jaipur Dental College, Jaipur. Clinical, radiological and histopathological parameters were recorded from the OPD files obtained from the Dept of Oral & Maxillofacial Surgery of Jaipur Dental College, Jaipur, Dept of General Surgery of SMS Medical College, Jaipur and Dept of Oral Pathology and Microbiology of Jaipur Dental College, Jaipur. The data of the patients were collected after attainment of written consent forms from the patients. A formal informed written consent was taken from all the patients.

Consent for publication: 'Not applicable' Availability of data and material: All data generated or analysed during this study are included in this published article. Competing interests: None

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