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Original Article

Dentistry Section

A Comparative Analysis of Cytokeratin 18 and 19 Expressions in Odontogenic Keratocyst, Dentigerous Cyst and Radicular Cyst with a Review of Literature

VIKAS PARSHOTTAM BHAKHAR[1], VANDANA SANDIP SHAH[2], MOHSIN JIVA GHANCHI[3], SANDESH SACHCHIDANAND GOSAVI[4], HIMANSHU MAHESH SRIVASTAVA[5], NIVEDITA JAVAHIR PACHORE[6]

ABSTRACT

Introduction: Odontogenic cysts viz Odontogenic Keratocyst (OKC), Dentigerous Cyst (DC) and Radicular Cyst (RC) occur commonly in the oral and maxillofacial region. Cytokeratin (CK) expression studies have been done to evaluate diagnostic accuracy, role in pathogenesis, elucidate behaviour and role in treatment protocols. However, variations have been reported in the expression of CK patterns in these odontogenic cysts, which could be due to the lack of standardization of laboratory techniques. The present study has tried to shed light on CK 18 and 19 expression in odontogenic cysts and offer the brief review of previous studies on these CK.

Aim: The aim of the present study was to evaluate the intensity and expression patterns of CK 18 and 19 in OKCs, DCs and RCs.

Materials and Methods: A total of 60 cases, 20 each of OKC, DC and RC were confirmed histologically and evaluated for immunohistochemical expression pattern and intensity of CK 18 and 19.

Results: A focal and variable expression of CK 18 was observed in 25% of OKCs, 15% of DCs and 10% of RCs. CK 19 was expressed in 75% of OKCs and 100% in DCs as well as RCs.

Conclusion: The intensity and expression of Cytokeratin 19 was more in all three cysts compared to Cytokeratin 18.

Keywords: Comparison, Diagnosis, Intensity

INTRODUCTION

Odontogenic cysts have been traditionally classified into developmental including Odontogenic Keratocysts (OKC), Dentigerous Cysts (DC) and inflammatory including Radicular Cysts (RC) [1,2]. The recent WHO classification has classified OKCs as Keratocystic Odontogenic Tumour (KCOT). However, till date there is no international consensus on its neoplastic nature or its renomenclature [3,4].

Odontogenic cysts are routinely diagnosed through clinical, radiological and histopathological examination. The histomorphology provides valuable information but at times these cysts may produce overlapping features making it difficult to arrive at a diagnosis. In such cases immunohistochemical expression of cytokeratins can aid in diagnosis of these cysts [5].

Cytokeratins (CK) or the intermediate filaments are considered to be the fundamental markers of differentiation of epithelial cells. Changes in their expression not only vary from region to region, but may also be modified by pathologic processes during histogenesis and tissue maturation [6]. Cytokeratin 18 (CK 18) is the lower molecular weight acidic cytokeratin which shows expression in histogenetic structures such as dental lamina and enamel epithelium along with expression in respiratory and oesophageal squamous epithelium [7]. Cytokeratin 19 (CK 19) is the smallest known acidic type of cytokeratin and is discernible in simple epithelia and basal cells of non-keratinized stratified squamous epithelia. It also shows an almost obligatory expression in all normal and pathological odontogenic epithelia like cell rests of Malassez, cell rests of Serre and junctional epithelium [8,9].

There are many studies which were done to determine the cytokeratin expression patterns in odontogenic cysts to establish their reliability as diagnostic markers. Researchers have however provided consistent results with regards to certain CK and contradictory results for other cytokeratins. Similarly highly variable results for CK 18 and 19 expressions in OKC, DC and RC have been obtained from existing literature search [10]. Hence the present study was planned to confirm the earlier research findings and a research hypothesis stating: CK 18 and 19 could prove valuable aid in diagnosis of OKC, DC and RC.

MATERIALS AND METHODS

Samples and Procedures: The study was conducted in the Department of Oral Pathology, K. M. Shah Dental College and Hospital, Sumandeep Vidyapeeth, in the month of January 2013. A total of 60 cases, 20 each of OKC, DC and RC with data including clinical characteristics, radiographic interpretations and confirmed histopathological diagnosis were retrieved from archives of the department. Evaluation was done for immunohistochemical expression of CK 18 (DAKO, Monoclonal mouse anti-human, RTU, clone DC 10) and CK 19 (DAKO, Monoclonal mouse anti-human, RTU, clone RCK 108). Both the CK products were RTU (Ready to Use), so they did not require dilution which assisted to maintain the uniformity.

Immunohistochemistry: Formalin-fixed, paraffin-embedded tissues sectioned at 4 microns thickness were obtained from each block and subjected to immunohistochemical staining by using Polymer Horseradish Peroxidise (poly-HRP) detection system. This system offers the great advantages such as 'minimal background noise' and 'minimal incubation time'. Antigen retrieval was carried out by 'heat induced antigen retrieval method' in which tissue sections were placed in pressure cooker along with 10 mM aqueous citrate buffer (pH 6.0) and pressure cooker operated at

120°C with full pressure. Tissue sections were then immersed in 3% hydrogen peroxidase for 10 min to block endogenous peroxidise and subsequently incubated with antibody to CK 18 and CK 19 overnight at 4ºC. HRP-labelled rabbit anti-mouse antibody was added to the tissue sections at room temperature for 1 hour. Reaction product was developed by adding 3, 3' Diaminobenzidine Tetrahydrochloride (DAB) to the tissue sections. Tissue sections were then counterstained with Haematoxylin and Eosin stain and evaluated under light microscope (LABOMED, CXR5) at a 100- and 250-fold magnification. Presence of brown end product at the site of target antigen indicated positive and absence of staining indicated negative immunoreactivity. Tissue sections of breast carcinoma were taken as positive control. The CK expressions were graded as negative, mild, moderate and intense as given in [Table/Fig-1]:

The expression patterns were further assessed as "ALL" or "FOCAL" as per specified below:

"ALL" Expression pattern - staining confined in entire layer of the epithelium. (Either basal, middle, upper or all the layers).

"FOCAL" expression pattern - staining confined in scatter areas of the epithelium. (Either basal, middle, upper or all the layers).

Each slide was scored independently by three different observers and inter-observer variability was calculated by using Kappa statistics test which was not found significant.

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS software (version 17, IBM Corporation, US). Z-test was done to compare the CK expressions of both CK among the three cysts and Pearson's chi-square test was done to evaluate the expression of each CK.

RESULTS

CK 18 expression was found positive in few of the 60 cases and mostly in OKCs compared to DC and RC. A "FOCAL" expression pattern with mild intensity was observed predominantly among these positive cases [Table/Fig-2-5]. CK 19 expression was positive in 100% of DC and RC and about 75% in OKC. An intense and "ALL" expression was predominant in DC and RC [Table/Fig-6-9] while moderate and "ALL" expression was found more in OKC [Table/Fig-10]. Some of the cases of DC and RC were recorded with moderate intensity and very few cases were reported with mild intensity [Table/Fig-11,12].

Comparison of CK 18 and CK 19 expression in odontogenic keratocysts was statistical significant (p-value-0.001) and in dentigerous cysts and radicular cysts it was highly significant. (DC, p-value-0.001), (RC, p-value-0.001) [Table/Fig-13].

'+'	Negative	No staining
'+'	Mild	Staining restricted to single epithelial layer.
'++'	Moderate	More than one layer of epithelium stained but not its entire thickness.
'+++'	Intense	staining in the entire thickness of epithelium.

[Table/Fig-1]: CK 18 and CK 19 intensity grading.

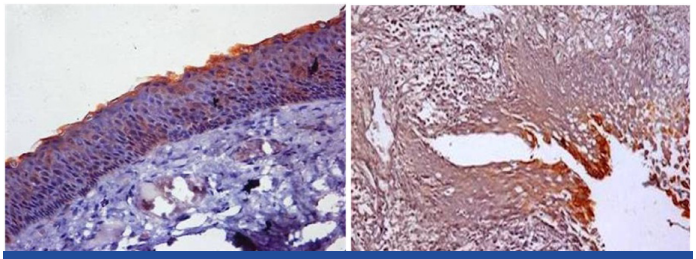
Cysts	Positive expression				Negative expression	Chi-square value	p-value
	+	++	+++	Total			
Odontogenic keratocyst 20 (100%)	4(80%)	1(20%)	0 (0%)	5(25%)	15 (75%)	2.947	0.567
Dentigerous cyst 20 (100%)	3(100%)	0(0%)	0 (0%)	3 (15%)	17 (85%)		
Radicular cyst 20 (100%)	2(100%)	0 (0%)	0 (0%)	2 (10%)	18 (90%)		

[Table/Fig-2]: Cytokeratin 18 expression in Odontogenic keratocyst, Dentigerous cyst and Radicular cyst.

DISCUSSION

CK are constituents of complex network extending from the surface of the nucleus to the peripheral cell sector where they get inserted into different cell junctions like desmosomes and hemidesmosomes. The presence of these CKs in tooth development has lent credence to suggestions that they have an active role in the embryonic development of the dental organ and hence, their expression in odontogenic cysts and tumours has been a subject of study for various authors. Identity of a cell as an epithelial cell and also its different stages during differentiation can be studied through the patterns of expression of keratins. The utility of CK 18 and 19 to identify odontogenic epithelium have been demonstrated by numerous biomedical studies and therefore in cases where an odontogenic origin of neoplasms or cysts is suspected, they have been proven to be a useful tool in diagnosis [11-13].

In the present study, CK 18 expression was found positive in 25% of OKCs. These findings are in contrast to Meara et al., who found CK 18 positive in 17% of OKC associated with Nevoid Basal Cell Carcinoma (NBCC) syndrome, and 57% in non syndromic OKCs [14]. Nevoid basal cell carcinoma is the syndrome which not only



[Table/Fig-4]: Photomicrograph of OKC showing cytokeratin 18 expression with mild (+) intensity and "FOCAL" distribution. (Upper cell layer) (40X magnification).
[Table/Fig-5]: Photomicrograph of RC showing cytokeratin 18 expression with mild (+) Intensity and "FOCAL" Distribution (Upper cell layer) (20X magnification).

Cysts	Positive expression				Negative expression	Chi-square value	p-value
	+	++	+++	Total			
Odontogenic keratocyst 20(100%)	4 (27%)	11(73%)	0 (0%)	15 (75%)	5 (25%)	26.128	0.000
Dentigerous cyst 20(100%)	2 (10%)	5 (25%)	13 (65%)	20 (100%)	0 (0%)		
Radicular cyst 20 (100%)	4 (20%)	7 (35%)	9 (45%)	20 (100%)	0 (0%)		

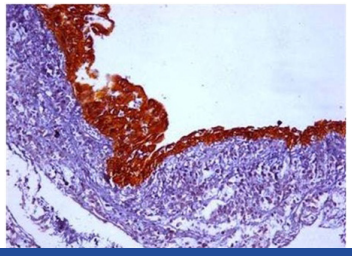
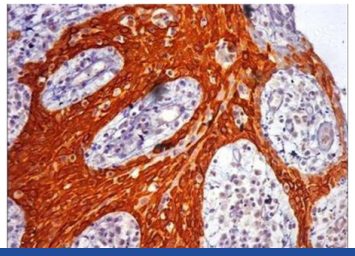
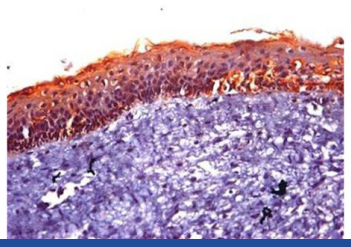
[Table/Fig-6]: Cytokeratin 19 expression in Odontogenic keratocyst, Dentigerous cyst and Radicular cyst.

Cysts	Epithelial layers (ALL Expression)				Chi-square value	p-value	Epithelial layers (FOCAL Expression)				Chi-square value	p-value
	Total	Basal	Middle	Upper			Total	Basal	Middle	Upper		
Odontogenic keratocyst 5 (25%)	2(40%)	0(0%)	2(100%)	1(50%)	NA*	NA*	3(60%)	0(0%)	0 (0%)	3(100%)	0.288	0.866
Dentigerous cyst 3 (15%)	0(0%)	0(0%)	0(0%)	0 (0%)			3(100%)	2 (67%)	0 (0%)	1 (33%)		
Radicular cyst 2 (10%)	0(0%)	0(0%)	0(0%)	0 (0%)			2(100%)	0 (0%)	1(50%)	1 (50%)		

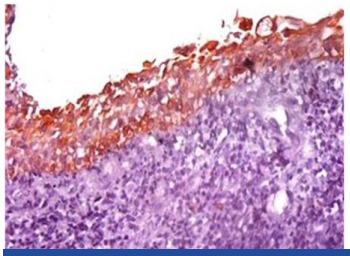
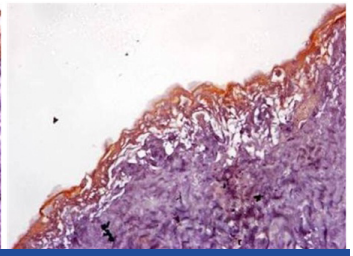
[Table/Fig-3]: Cytokeratin 18 positive expression patterns within the epithelial layers.
*NA-Not available

Cysts	Epithelial layers (ALL Expression)				Chi-square value	p-value	Epithelial layers (FOCAL Expression)				Chi-square value	p-value
	Total	Basal	Middle	Upper			Total	Basal	Middle	Upper		
Odontogenic keratocyst 15 (75%)	10(67%)	9(90%)	7(70%)	3 (30%)	10.133	0.006	5(33%)	3(60%)	3(60%)	2(40%)	0.784	0.676
Dentigerous cyst 20 (100%)	18(90%)	17(94%)	14(78%)	16(89%)			2(10%)	2(100%)	2(100%)	0 (0%)		
Radicular cyst 20 (100%)	17(85%)	12(71%)	15(88%)	16(94%)			3(15%)	2(67%)	1(33%)	1(33%)		

[Table/Fig-7]: Cytokeratin 19 positive expression patterns within the epithelial layers.

[Table/Fig-8]: Photomicrograph of DC showing cytokeratin 19 expression with intense (+++) intensity and "ALL" distribution (basal, middle and upper cell layer) (20Xmagnification). **[Table/Fig-9]:** Photomicrograph of RC showing cytokeratin 19 expression with intense (+++) intensity and "ALL" distribution (basal, middle and upper cell layer) (40X magnification). **[Table/Fig-10]:** Photomicrograph of OKC showing cytokeratin 19 expression with moderate (++) intensity and "ALL" distribution (basal and upper cell layer) (40X magnification).

[Table/Fig-11]: Photomicrograph of DC showing cytokeratin 19 expression with moderate (++) intensity and "ALL" distribution. (basal and upper cell layer) (40X magnification). **[Table/Fig-12]:** Photomicrograph of DC showing cytokeratin 19 expression with mild (+) intensity and "ALL" distribution. (upper cell layer) (40X magnification).

Cysts	Cytokeratin 18	Cytokeratin 19	Z-test	p-value
Odontogenic keratocyst	5(25%)	15 (75%)	3.65	0.001
Dentigerous cyst	3 (15%)	20 (100%)	10.65	0.001
Radicular cyst	2 (10%)	20 (100%)	13.42	0.001

[Table/Fig-13]: Comparison of Cytokeratin 18 and Cytokeratin 19 in Odontogenic keratocyst, Dentigerous cyst and Radicular cyst.

includes OKC but also other defects within multiple body systems such as the skin, nervous system, eyes, endocrine system and bones. Because keratin expression is generally regulated by cell activation and differentiation, it can be inferred that its expression may shed light on the differentiation trends of skin neoplasms. That's why in such cases variations are found within KC expression pattern. Apart from that, technique sensitivity also plays an important role in variation regarding the expression pattern, hence the variation in results.

MacDonald and Fletcher reported 100% positivity with monoclonal antibody LP 34 in OKC and DC but Brown et al., suggested that LP 34 stains CK other than Ck 18 too. Furthermore LP 34 reactivity in paraffin sections of OKCs is particularly laboratory and technique dependent [15,16]. Santos et al., noted CK 18 expression within basal cell layer but in NBCC syndromic cases, while Hormia et al., did not find any positive case in their study [17,18].

CK 18 positivity in the present study was found in 15% of DC and 10% in RC. Meara et al., reported 75% and Hormia et al., found 50% positive cases in their study, while Mathews et al., Gao et al., and Shruthi et al., reported all the cases negative [14,18-21].

A "FOCAL" expression within the basal and upper cell layers was observed in DCs and in the middle and upper cell layers in RCs similar to Meara et al., who reported a predominant "FOCAL" expression pattern in upper cell layers [14]. These noticeable differences observed in the expression pattern of CK 18 in DC could not only be attributed to the specific histogenic origin and distinct functional characteristics of cells but alternately could also be a sign of oncofetal transformations [18]. In RC, metaplastic epithelial changes within the epithelium could be a plausible explanation for their expression [22].

CK 19 expression was positive in 75% of OKCs, finding in accordance with those of Hormia et al., Gao et al., Morgan et al., Matthews et al., Li et al., Hayakawa et al., Tsuji et al., Dos santos et al., Aragaki et al., Kamath et al., and Yarlagadda et al., who reported nearly all the cases positive with CK 19 [7,13,17-20,23-27]. However in contrast Stoll et al., Wagner et al., and de Berardinis et al., found negative expressions in their studies [5,28,29].

About 67% positive cases showed an "ALL" expression pattern predominantly within basal and middle cell layers and 33% cases depicted "FOCAL" expression pattern mainly within superficial cell layers. Similarly CK 19 expression was noted in all layers of epithelia but predominantly in basal and few suprabasal cells in the study of Hormia et al., Gao et al., and Aragaki et al., in superficial and spinous cell layer as reported by Hayakawa et al., Tsuji et al., and Kitano et al., in superficial and basal cells by Yarlagadda et al., and in superficial cells by Kamath et al., [13,18,20,23-27]. The fact that CK 19 is a minor component of basal cells of stratified squamous epithelia could be one of the possible explanations for the predominant expression in basal cell layer [7].

CK 19 expression was 100% positive in both DCs and RCs, similar to the findings of Hormia et al., Gao et al., Morgan et al., and Tsuji et al., who also reported nearly all the cases positive with CK 19 [7,18,20,25]. On the other hand Stoll et al., found 50% positive cases in DC and 47% cases in RC, while Wagner et al., recorded 48% positive cases in both the cysts [5,28].

An "ALL" expression pattern in the entire epithelial layer was seen in 90% of DCs and 85% of RCs, similar to the findings of Hormia et al., Morgan et al., Mathhews et al., and Gao et al., who also found the expression of CK 19 in all the layers of DC [7,18-20]. Tsuji et al., Stoll et al., and Kamath et al., noted predominant expression in the superficial cell layer and Katuri et al., noted in basal cells in DCs [5,25,27,30]. Also, Gao et al., Katuri et al., and Tsuji et al., reported higher expression in superficial cell layers, Stoll et al., in suprabasal cells and De berardinis et al., reported strong positivity in the basal and parabasal layers in RC [5,20,25,29,30].

However, certain minor differences observed in expression within cell layers of these cysts could be explained by proliferating odontogenic epithelium which exhibits certain phenotypical

differences when compared to normal epithelia [31]. Gradual maturation of the epithelial cells as they migrate to upper layers (basal to apical differentiation) could result in expression of CK 19 in OKC, a fact which is unobserved in dentigerous and radicular cysts [18].

Since there is always a possibility that masking of some or all epitopes on a particular keratin in certain cells can occur, Smith et al., and Mathhews et al., emphasized the need for care in the interpretation of negative results in immunocytochemistry, particularly in studies of keratins. Further, differences in reactivity between different monoclonal antibodies for the same keratin were well documented and this was certainly the case with CK 19 and CK 18 [32]. A comparative table of various studies has been presented in [Table/Fig-14,15].

Authors (Years)	Odontogenic Keratocyst	Dentigerous cyst	Radicular cyst
Hormia et al., [18] (1987)	No reactivity noted with antibody PKK3 and K_s18.18 for cytokeratin 18 in simple epithelia	A distinct layer of positive cells were noted with antibody PKK3 and K_s18.18 for cytokeratin 18 in simple epithelia	No reactivity noted with antibody PKK3 and K_s18.18 for cytokeratin 18 in simple epithelia
Matthews et al., [19] (1988)	No Expression was observed	No expression was observed	Rare expression was observed in the superficial cells in areas of mucous metaplasia
Gao et al., [20] (1989)	No staining reaction was noted with mAb LE61 for K 18 in simple epithelia	The mAbs against K 18 either failed to react or only reacted weakly with the epithelium	Not Described
Meara et al., [14] (2000)	Trace staining with Focal expression pattern mainly in the upper cell layer in OKC without NBCC syndrome cases, while No staining was noted in OKC with NBCC syndrome	Positive expression was noted, albeit weakly and inconsistently. The pattern and intensity was too inconsistent to draw any diagnostic conclusion.	Not studied
Shruthi et al., [21] (2014)	Found negative in all the cases		

[Table/Fig-14]: Expression of CK 18 in OKC, DC and RC in previous studies.

Authors (Years)	Odontogenic Keratocyst	Dentigerous cyst	Radicular cyst
Hormia et al., [18] (1987)	PKK2 for CK 7, 17, 19 gave bright staining throughout all the epithelial layers	PKK2 for CK 7, 17, 19 reacted with all the cell layers of epithelium	PKK2 for CK 7, 17, 19 reacted with all the cell layers of epithelium
Morgan et al., [7] (1987)	LP2K for CK 19 expressed at all levels of the epithelium	LP2K for CK 19 stained most of the cells at all levels of the epithelium	
Matthews et al., (1988) [19]	CK 19 ('simple') strong reactivity within epithelial cell layer	CK 19 ('simple') strong reactivity within epithelial cell layer	CK 19 ('simple') strong reactivity within epithelial cell layer
Mcdonald & Fletcher [15] (1989)	LP 34 antibody reactivity found negative for basal cells while moderately to strongly positive for other cell layers	LP 34 antibody reactivity found positive for all the cell layers	
Matthews and Browne [16] (1989)	Did not notice the reactivity of LP 34, so raised uncertainty against the result of Mcdonald and Fletcher		
Mcdonald & Fletcher [15] (1989)	Response to Matthews and Browne Highlight on the need for standardised technique		
Gao et al., [20] (1989)	Patchy staining reaction predominantly with suprabasal cells and some basal cell	Strongly positive staining reaction either with full thickness of epithelium or with superficial cells	
Kitano et al., [23] (1998)	Reactivity to AE1 antibody (Acidic, Type 1, Cytokeratin) was limited to the upper suprabasal and surface parakeratinized cell layers.		
Wagner et al., [28] (1999)	No expression was noted	Found positive expression but not specified layers	Found positive expression but not specified layers
Stoll et al., [5] (2005)	Completely Negative	Positive staining observed in all the cell layers but predominantly within superficial cell layer	Positive staining observed in all the cell layers but predominantly within suprabasal cell layer
Okada et al., [24] (2006)	Almost entirely positively expressed in the superficial and spinous cell layer in KCOT		
Santos [17] (2009)	Strong expression was noted affecting mainly suprabasal and intermediate layer cells.		
Aragaki et al., [26] (2010)	Strong positive expression predominantly observed in basal and suprabasal cells.		
Tsuji [25] (2014)	Expression was noted predominantly within superficial cell layer followed by spinous cell layer followed by basal cell layer	Expression was observed predominantly within superficial cell layer followed by spinous cell layer followed by basal cell layer	Expression was observed predominantly within superficial cell layer followed by spinous cell layer followed by basal cell layer
Katuri et al., [30] (2015)	Slightly positivity noted in all the cell layers	Positive expression was noted in all the cell layers Mean number of positive basal cells were predominant	Positive expression was noted in all the cell layers Mean number of positive suprabasal cells and superficial cells were predominant
Kamath et al., [27] (2015)	Predominant expression staining grade was negative and '+' with less extent of '++'. Positive specimen showed staining mainly within superficial cells of epithelium	Predominant expression staining grade was '++' and '+++' with less extent of '+'. Positive specimen showed staining mainly within superficial and suprabasal cells of epithelium	
Yarlagadda et al., (2015) [13]	Consistently positive throughout the epithelium lining and diffuse staining pattern in superficial cell layer and basal cell layer	Homogenous expression within all the cell layer	Diffuse staining reaction in all the cell layers of epithelium

[Table/Fig-15]: Expression of CK 19 in OKC, DC and RC in previous studies.

CONCLUSION

CK 18 and 19 expressions in OKC, DC and RC thus could prove valuable aid in diagnosis of these wherever overlapping features pose a problem. Furthermore, the differences in reports of expressions of CK 18 & CK 19 in OKC, DC and RC by different researchers may be due to different antigen retrieval methods used, different monoclonal antibodies used, or the smaller sample size. Also standardization of laboratory techniques could help in gaining a deeper insight into behaviour as well as pathogenesis of these lesions.

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PARTICULARS OF CONTRIBUTORS:

1. Senior Lecturer, Department of Oral Pathology, College of Dental Science, Bhavnagar, Gujarat, India.
2. Professor and Head, Department of Oral Pathology, K. M. Shah Dental College, Vadodara, Gujarat, India.
3. Professor and Head, Department of Oral Pathology, College of Dental Science, Bhavnagar, Gujarat, India.
4. Dean, College of Dental Science, Bhavnagar, Gujarat, India.
5. Post Graduate Student, Department of Oral Pathology, K. M. Shah Dental College, Vadodara, Gujarat, India.
6. Senior Lecturer, Department of Prosthodontics, College of Dental Science, Bhavnagar, Gujarat, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Vikas Parshottam Bhakhar,
10, Kapidhwaj Bunglow, Near Shraddha School, Jodhpurgam Road, Satellite, Ahmedabad-380015, Gujarat, India.
E-mail: vikas873@yahoo.com

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