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ORIGINAL ARTICLE

Mast Cells in Odontogenic Cysts

SHYLAJA S

ABSTRACT

Background: Cysts of the jaws are probably the most common destructive bone lesions in the human maxillofacial skeleton. Odontogenic cysts are derived from the epithelium which is associated with the development of the dental apparatus and can be either developmental or inflammatory in origin. The most common odontogenic cysts are radicular cysts, dentigerous cysts and odontogenic keratocysts. However, the cysts of developmental origin may show inflammatory changes secondary to infection. Mast cell degranulation plays an important role in the inflammatory response and it is speculated that alteration in their number and distribution could contribute to the pathogenesis of odontogenic cysts. So, an attempt was made to evaluate the significance and distribution of mast cells in radicular cyst, odontogenic keratocyst and dentigerous cyst using toluidine blue staining.

Materials and Methods: This retrospective study was undertaken by retrieving the records and the paraffin blocks of 40 confirmed cases of odontogenic cysts, out of which 19 were Radicular cysts, 12 were odontogenic keratocysts and 9 were dentigerous cysts.

Sections of 5µm thickness were prepared and stained with haematoxylin and eosin, as well as with toluidine blue. The toluidine blue stained mast cells were then counted under a high power microscopic field (40X) for each specimen in three different zones and the mean value obtained. The mean number of mast cells was then compared between different zones by using the Relative Deviate 'Z' test.

Results: In cases of radicular cyst, the highest mean number of mast cells per high power field was seen in the age group of 10-19 years. A statistically significant difference ($p<0.05$) amongst the distribution of mast cells was noted between the sub-epithelial and the deep zones. In cases of odontogenic keratocyst, the highest mean number of mast cells per high power field was seen in the age group of 20-29 years. A statistically significant difference ($p<0.01$) amongst the distribution of mast cells was noted between the sub-epithelial and the deep zones, as well as between the sub-epithelial and the intermediate zones. In cases of dentigerous cyst, the highest mean number of mast cells per high power field was seen in the age group of 10-19 years. A statistically significant difference ($p<0.05$) amongst the distribution of mast cells was noted between the sub-epithelial and the deep zones.

Conclusion: In the present study, the maximum number of mast cells were noted in the sub-epithelial zone as compared to other zones. The number of mast cells were seen to decrease with age and there was no gender predilection. However, further studies using immunohistochemical techniques may help in the better understanding of the pathogenesis of these cysts.

Key Words: Mast cells, Odontogenic cysts, Radicular Cyst, Odontogenic Keratocyst, Dentigerous cyst, Toluidine blue.

Department of Oral & Maxillofacial Pathology SVS Institute of Dental Sciences Mahabubnagar,Andhra-Pradesh (INDIA).
Corresponding Author:
Dr. Sanjeevareddigari Shylaja
MIG-276, 4th road, KPHB Colony, Kukatpally, Hyderabad-500072(INDIA)
Phone No. - 09441023999
Email id: eshwardental@rediffmail.com

Introduction

Cysts of the jaws are probably the most common destructive bone lesions in the human maxillofacial skeleton. The head and neck region and the jaw in particular, collectively comprise one of the most common sites for the occurrence of cysts [1].

Odontogenic cysts are derived from the epithelium which is associated with the development of the dental apparatus. They are either of developmental origin or may result from inflammation. The most common odontogenic cysts are radicular cysts, odontogenic keratocysts and dentigerous cysts [2].

Cystic expansion is influenced by a number of factors like mural growth, hydrostatic enlargement and bone resorbing factor. The hydrostatic pressure of the luminal fluid is important in cyst enlargement and mast cell activity might contribute to this by increasing the osmotic pressure of the fluid [3].

Mast cells have been the object of investigation for almost a century, but still remains an enigma in terms of their function in situ. They have often puzzled investigators from the time that they were first identified and were named by Ehrlich in 1887 [4].

Mast cells are present in mucosal and connective tissue environments. They possess cytoplasmic granules that stain meta-chromatically under ordinary conditions [5]. Degranulations of mast cells play an important role in the initiation of the inflammatory response. This action is significant in the pathogenesis of different lesions like lichen planus, early periodontal diseases, ulcerative colitis, pulmonary fibrosis, inflammatory bowel, systemic mastocytosis and odontogenic cysts [6].

Mast cells are recognized in non-keratinizing and keratinizing odontogenic cysts. Alteration in their number and distribution could contribute to the pathogenesis of odontogenic cysts [3]. The special stains used for mast cell staining are toluidine blue, azur A, bismark brown, thionin and alcian blue [7].

Mast cells might play a role in the pathogenesis of odontogenic cysts. So, an attempt was made to evaluate the significance and distribution of mast

cells in radicular cysts, odontogenic keratocysts and dentigerous cysts by using toluidine blue staining.

Aims and Objectives

To study the presence and the number of mast cells in radicular cysts, odontogenic keratocysts and dentigerous cysts. To evaluate the distribution of mast cells in the subepithelial, intermediate and deep zones. To correlate the number of mast cells and their distribution with age, sex and the different zones which were considered.

Materials and Methods

This retrospective study was undertaken by retrieving the records and the paraffin blocks of confirmed cases of odontogenic cysts. The paraffin blocks were sectioned and stained with haematoxylin and eosin and toluidine blue. A total of 40 cases were included in this study, out of which 19 were radicular cysts, 12 were odontogenic keratocysts and 9 were dentigerous cysts.

Mast cell count was done in sections which were stained with toluidine blue. Four areas were randomly selected under a high power field (40x) for each specimen. The area encompassed by one high power field (HPF) was taken as one microscopic field (MF). In each area, three zones were considered. The subepithelial zone was the area just below the epithelium and the next two consecutive microscopic fields were the intermediate and the deep zones.

Statistical Analysis

The number of mast cells per microscopic field for individual cyst was calculated at the three zones and the means (±S.D) for each type of cyst were taken. The mean number of mast cells were compared between the different zones by using the Relative Deviate 'Z' test.

Results and Observations

Out of the total 40 cases, 30 were males and 10 were females.

Age

In radicular cysts, the age ranged from 7 to 48 years. The maximum number of cases were in the age group of 10 to 19 years (8 cases). In odontogenic keratocysts, the age ranged from 15 to 58 years. The maximum number of cases were in the age group of 20 to 29 years (10 cases). In dentigerous cysts, the age ranged from 11 to 45 years. The maximum number of cases were in the age group of 10 to 19 years (4 cases) [Table / Fig 1].

Sex

Out of 19 cases of radicular cysts, 12 (63.2%) were males and 7 (36.8%) were females, with a male to female ratio of 1.7:1. Out of 12 cases of odontogenic keratocysts, 10 (83.3%) were males and 2 (16.7%) were females, with a male to female ratio of 5:1. Out of 9 cases of dentigerous cysts, 8 (88.9%) were males and 1 (11.1%) was a female, with a male to female ratio of 8:1 [Table / Fig 1].

(Table / Fig 1) Age and Sex-Wise Distribution of Mast Cells in Odontogenic Cysts

Age Group (Years)	Radicular Cyst		Odontogenic Keratocyst		Dentigerous Cyst	
	Males	Females	Males	Females	Males	Females
0-9	2	0	0	0	0	0
10-19	5	3	1	0	4	0
20-29	4	3	8	2	1	0
30-39	0	1	0	0	3	0
40-49	1	0	0	0	0	1
50-59	0	0	1	0	0	0
Total	12	07	10	02	08	01

Mast Cell Distribution

Age Wise Distribution of Mast Cells

In radicular cysts, the mean number of mast cells per HPF was high in the age group of 10 to 19 years [Table / Fig 2] (Table 2). In odontogenic keratocysts, the mean number of mast cells per HPF was high in the age group of 20 to 29 years [Table/Fig 2] (Table 3). In dentigerous cysts, the mean number of mast cells per HPF was high in the age group of 10 to 19 years [Table / Fig 2] (Table 4).

(Table/Fig 2) Table2: Age Wise Distribution Of Mast Cells In Radicular Cyst

Age (years)	No. of cases	No. of fields	Total no. of mast cells	Mast cells/HPF (Mean ±S.D.)
0 -9	2	24	89	3.71 ± 4.91
10 - 19	8	96	416	4.33 ± 5.55
20 - 29	7	84	226	2.69 ± 4.26
30 - 39	1	12	5	0.42 ± 0.67
40 – 49	1	12	24	2.00 ± 1.27
50 - 59	0	0	0	-
Total	19	228	760	3.33 ± 4.84

(Table/Fig 2) Table 3: Age Wise Distribution Of Mast Cells In Odontogenic Keratocyst

Age (years)	No. of cases	No. of fields	Total no of mast cells	Mast cells/HPF (Mean ± S.D.)
0 -9	0	0	0	-
10 - 19	1	12	8	0.67 ± 0.79
20 - 29	10	120	554	4.62 ± 6.95
30 - 39	0	0	0	-
40 – 49	0	0	0	-
50 - 59	1	12	17	1.42 ± 1.62
Total	12	144	579	4.03 ± 6.51

(Table/Fig 2) Table 4: Age Wise Distribution Of Mast Cells In Dentigerous Cysts

Age (years)	No. of cases	No of fields	Total no. of mast cells	Mast cells/HPF (Mean ± S.D.)
0 -9	0	0	0	-
10 - 19	4	48	188	3.92 ± 4.64
20 - 29	1	12	34	2.83 ± 3.41
30 - 39	3	36	50	1.39 ± 1.70
40 – 49	1	12	22	1.83 ± 1.85
50 - 59	0	0	0	-
total	9	108	294	2.71 ± 3.66

Sex Wise Distribution of Mast Cells

In all the three cysts, statistically significant differences was not noted in the distribution of mast cells between males and females [Table/ Fig 3] (Table 5), (Table 6), (Table 7).

(Table/Fig 3) Table 5: Sex Wise Distribution of Mast Cells in Radicular Cyst

Sex	No. of cases	No. of fields	Total mast cells	Mast cells/HPF	Significance	
					Z Value	P Value
Males	12	144	454	3.15 ± 4.20	0.68	N.S.
Females	7	84	306	3.64 ± 5.77		
Total	19	228	760	3.33 ± 4.84		

(Table/Fig 3) Table 6: Sex Wise Distribution of Mast Cells in Odontogenic Keratocyst

Sex	No. of cases	No. of fields	Total mast cells	Mast cells/HPF	Significance	
					Z Value	P Value
Males	10	120	490	4.1 ± 6.94	0.41	N.S.
Females	2	24	89	3.71 ± 3.56		
Total	12	144	579	4.03 ± 6.51		

(Table/Fig 3) Table 7: Sex Wise Distribution of Mast Cells in Dentigerous Cysts

Sex	No. of Cases	No. of fields	Total mast cells	Mast cells/HPF	Significance	
					Z Value	P Value
Males	8	96	272	2.83 ± 3.82	1.51	N.S.
Females	1	12	72	1.83 ± 1.85		
Total	9	108	294	2.71 ± 3.66		

Zone Wise Distribution of Mast Cells

In radicular cysts, the mean number of mast cells per HPF was high in the subepithelial zone as compared to the intermediate and deep zones. A statistically significant difference ($P<0.05$) was noted between the subepithelial and the intermediate zones [Table/Fig 4](Table 8).

In odontogenic keratocysts, the mean number of mast cells per HPF was high in the subepithelial zone as compared to

the intermediate and the deep zones. A statistically significant difference (P<0.01) was noted between the subepithelial and the intermediate zones and between the subepithelial and the deep zones [Table/Fig 4](Table 9).

In dentigerous cysts, the mean number of mast cells per HPF was high in the subepithelial zone as compared to the intermediate and the deep zones. A statistically significant difference (P<0.05) was noted between the subepithelial and the deep zones [Table/Fig 4](Table10).

(Table/Fig 4) Table 8: Zone Wise Distribution Of Mast Cells In Radicular Cysts

Zones	No. of fields	Total No. of mast cells	No. of mast cells/HPF	Significance	
				Zones Compared	P Value
Subepithelial	76	353	4.64 ± 6.16	SEZ Vs IZ	N.S.
Intermediate	76	224	2.95 ± 4.32	SEZ Vs DZ	P<0.05
Deep	76	183	2.41 ± 3.35	IZ Vs DZ	N.S.
Total	228	760	3.33 ± 4.84		

SEZ – Subepithelial Zone; IZ – Intermediate Zone; DZ – Deep Zone.

(Table/Fig 4) Table 9: Zone Wise Distribution of Mast Cells in Odontogenic Keratocysts

Zones	No. of fields	Total No. of mast cells	No. of mast cells/HPF	Significance	
				Zones Compared	P Value
Subepithelial	48	328	6.83 ± 9.56	SEZ Vs IZ	P<0.01
Intermediate	48	128	2.76 ± 3.34	SEZ Vs DZ	P<0.01
Deep	48	123	2.60 ± 3.55	IZ Vs DZ	N.S.
Total	144	579	4.03 ± 6.51		

(Table/Fig 4) Table 10: Zone Wise Distribution of Mast Cells in Dentigerous Cysts

Zones	No. of fields	Total No. of mast cells	No. of mast cells/HPF	Significance	
				Zones Compared	P Value
Subepithelial	36	144	4 ± 5.09	SEZ Vs IZ	N.S.
Intermediate	36	92	2.55 ± 2.49	SEZ Vs DZ	P<0.05
Deep	36	58	1.61 ± 2.29	IZ Vs DZ	N.S.
Total	108	294	2.71 ± 3.66		

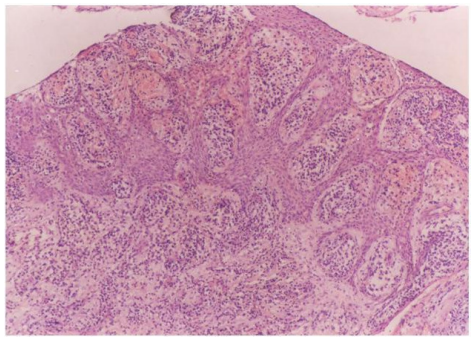
Comparison of Mast Cells between Odontogenic Cysts

Statistically significant differences was not noted in the distribution of the mast cells between the cysts when the zones are compared [Table/Fig 4] (Table 11),[Table/Fig 5] (Fig12), (Fig13), (Fig 14), (Fig15), (Fig16), (Fig 17).

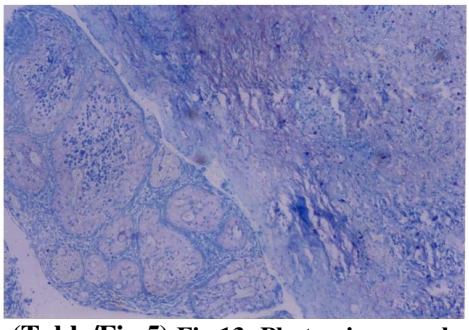
(Table/Fig 4) Table 11: Comparison of Mast Cells between Odontogenic Cysts

Zones	OKC	DC	RC	Diff. Between Cysts		
				OKC Vs DC	OKC Vs RC	DC Vs RC
Subepithelial	6.83 ± 9.56	4 ± 5.09	4.64 ± 6.16	N.S.	N.S.	N.S.
Intermediate	2.67 ± 3.34	2.55 ± 2.49	2.95 ± 4.32	N.S.	N.S.	N.S.
Deep	2.60 ± 3.35	1.61 ± 2.29	2.41 ± 3.35	N.S.	N.S.	N.S.

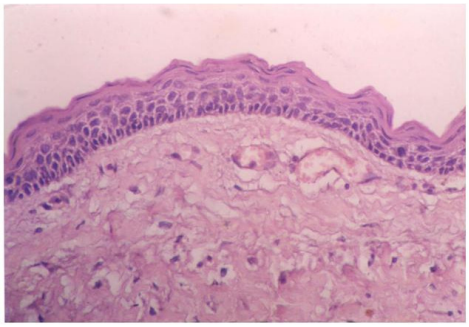
OKC – Odontogenic Keratocyst; DC – Dentigerous Cyst;
RC – Radicular Cyst



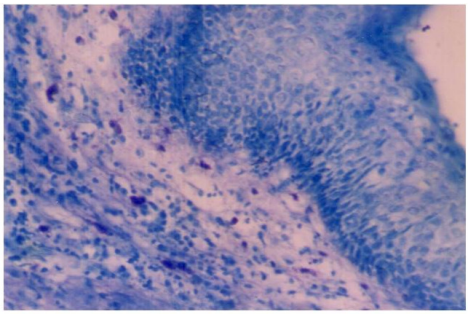
(Table/Fig 5) Fig 12: Photomicrograph Of H & E Stained Section Of Radicular Cyst (10x).



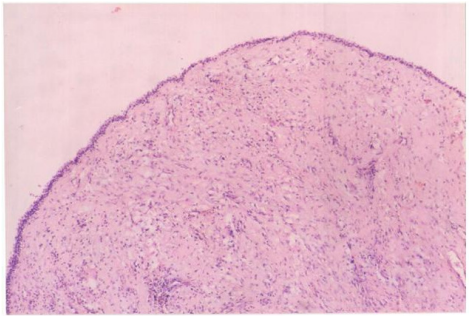
(Table/Fig 5) Fig 13: Photomicrograph Of Toluidine Blue Stained Section Of Radicular Cyst Showing Mast Cells (10x).



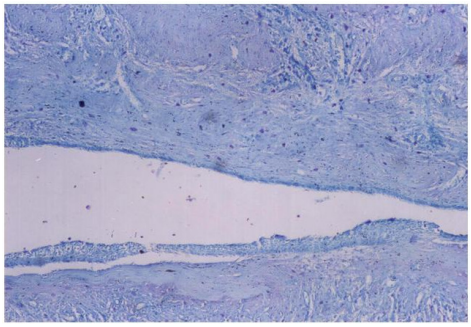
(Table/Fig 5) Fig 14: Photomicrograph Of H & E Stained Section Of Odontogenic Keratocyst (40x).



(Table/Fig 5) Fig15: Photomicrograph Of Toluidine Blue Stained Section Of Odontogenic Keratocyst Showing Mast Cells (40x).



(Table/Fig 5) Fig 16: Photomicrograph Of H & E Stained Section Of Dentigerous Cyst (20x).



(Table/Fig 5) Fig 17: Photomicrograph Of Toluidine Blue Stained Section Of Dentigerous Cyst Showing Mast Cells (10x).

Discussion

Mast cells are the normal members of the cell population in fibrillar connective tissue. For three quarters of a century, mast cells were biological curiosities. Few people knew anything about them, their contents and functions, though occasionally, few investigators made some studies without any conclusive results. In recent years, mast cells have received increasing attention and a number of investigations and reviews have appeared in the literature. With the advent of new techniques, various attempts have been made to study the response of these cells in physiological and different pathological conditions [8].

The mast cells in Hand E stained sections showed predominantly abundant basophilic granules and with toluidine blue, the mast cells stained red-purple (metachromatic staining) and the rest of the section stained blue. Mast cells can be confused with basophils. The functional and the biochemical characteristics of both the cells are much identical. A distinction between mast cells and basophils can be made upon

morphology, natural history, and by the expression of cell surface structures. Other cells that have been confused with mast cells include immature eosinophils or eosinophilic melanocytes and macrophages [14].

Mast cells might play a role in the pathogenesis of odontogenic cysts [9]. They contribute to cyst enlargement by increasing the osmotic pressure of the fluid at least in three ways 1) by direct release of heparin into the luminal fluid, 2) by release of hydrolytic enzymes which could degrade capsular extracellular matrix components, thereby facilitating their passage into the fluid and by the action of histamine on smooth muscle contraction and vascular permeability, thus encouraging the transudation of serum proteins [10]. Degranulation of mast cells has been implicated in the generation of prostaglandins, which would promote bone resorption and remodeling to accommodate the growing cyst [11]. Because of their possible importance in the pathogenesis of odontogenic cysts, an attempt was made to evaluate the presence and distribution of mast cells in the connective tissue and to correlate this data with age, sex, and the different zones considered.

When the age groups were compared in all the three cysts, the mean number of mast cells per HPF showed progressive decrease with age.

Although there are no studies mentioning the correlation between mast cell count and age in odontogenic cysts, in general, it was noted that mast cell count decreases in the connective tissue with age, as noted by some authors. **Matsson L** (**1993**) (12) and **Sjolin K.E** (**1946**) [13] showed that in man, there was a decrease in the number of dermal mast cells with increasing age from childhood to adults. **Wolf J.E et al.** (**1973**) [14] noted a decrease in the number of mast cells with age in germfree rats in the connective tissue of mandibular alveolar mucosa and bone marrow. This decrease in the number of mast cells with age could be due to increasing degranulation which is noted in older age [14]. **Abdel et al.** (**1976**) [15] reported an increase in the human dermal mast cells from 5 to 15 years of age, followed by a gradual decrease.

Matsson L. (**1993**) [12] noted a decrease in the number of mast cells from juvenile to adult rats in the tongue, buccal mucosa and gingival mucosa. The high number of mast cells in various oral sites of juvenile rats suggested that the oral mucosa of growing animals have a higher readiness for reaction, where mast cells take an active part than that of adults.

It is a pure conjecture, whether the reduced number of mast cells with increasing age in all the three odontogenic cysts is a result of the normal aging process or whether it is related to the pathogenesis of these cysts. So, further studies have to be carried out to know whether it is related to age or whether some other factors are responsible. Mast cell count varies between species. Therefore, studies of possible age variation in the mast cell population in the oral mucosa of man are needed.

In the present study, no statistically significant difference was noted in the

mast cell count between the sexes in all the three odontogenic cysts. **Coleman E.J** (**1974**) [16] noted no statistical difference in the mast cell count between males and females in hamster gingiva.

In the present study, the number of mast cells was more in the subepithelial zone as compared to the intermediate and deep zones in all the three odontogenic cysts. The difference in the distribution of mast cells between the subepithelial and deep zones was statistically significant ($P<0.05$) in all the three odontogenic cysts. In odontogenic keratocysts, a statistically significant difference ($P<0.01$) was noted in the subepithelial and the intermediate zones. This is compatible with that the reports of **Smith G. et al.**(**1989**) [9] who also noted a statistically significant difference ($P< 0.05$) between the subepithelial and the deep zones of all the three odontogenic cysts and also between the subepithelial and the intermediate zones in case of odontogenic keratocysts.

The subepithelial collection of mast cells in odontogenic cysts could be attributed to the chemotactic stimulus to mast cells, attracting them to the epithelial lining or luminal fluid contents. The nature of such stimulus is unclear, but the secretory matrix proteins of the normal odontogenic epithelium have been reported to be chemotactic to mast cells. Although odontogenic cysts are not known to secrete enamel matrix proteins, the epithelial lining stains positively for keratins and has been shown to share common antigenic determinants with enamel matrix proteins [9].

Smith G. et al. (**1988**) [3], in their histochemical studies on glycosaminoglycans of odontogenic cysts, observed a subepithelial band of alcian blue staining and this appeared to be due to the presence of heparin, which could have been released by the degranulation of mast cells beneath the epithelium to produce this staining pattern.

In the present study, a statistically significant difference was not noted between other zones like the subepithelial and the intermediate zones, and between the intermediate and the deep zones, except for odontogenic keratocysts which showed a statistically significant difference ($P<0.01$) between the subepithelial and the intermediate zones. This is in contrast to the reports by **Smith G. et al.** (**1989**) [9] who noted a significant difference ($P<0.05$) between the above mentioned zones.

Smith G. et al. (**1989**) [9] also noted a statistically significant difference ($P<0.03$) in the subepithelial zones of radicular cysts and odontogenic keratocysts, which was not observed in the present study.

These differences could be attributed to the specificity of the avidian-peroxidase staining as compared to the toluidine blue staining. They found that the avidin peroxidase stain was specific for mast cells and the differentiation of the mast cells from other tissue elements was good, because there was no staining on other cells of the inflammatory infiltrate or the connective extracellular matrix. Toluidine blue was not found to be effective due to poor metachromasia,

probably arising from acid decalcification of the tissue.

Several reasons may account for the difficulty to compare the data of different studies, like size of the sample, type of tissue examined, the method of fixation, the type of staining used, the morphological criteria of the mast cells considered by the investigator, the method used for counting the cells, the number of cells examined per biopsy, or maybe the investigated tissue area was too small to reduce the possible error caused by the inhomogeneity of cellular distribution [17], [18].

Schwartz J. and Dibble M. (**1975**) (19) and **Teronen O. et al.** (**1996**) [20] observed that toluidine blue, the routinely used special stain for mast cells, does not stain degranulated mast cells (phantom cells). This might lead to variations in the number of mast cells observed in the different zones.

Degranulated mast cells can be detected by immunohistochemical staining by using monoclonal antihuman tryptase antibodies and Western blotting by using specific antihuman mast cell tryptase antiserum [20].

Teronen O (**1996**) [20] noted that the density of intact mast cells decreased outwards from the cyst lumen. Degranulated mast cells were highest at the periphery of the cysts, at their border with bones, indicating higher activity of mast cells in this area. This was observed using immunohistochemical staining of mast cell tryptase.

Bischoff S.C.et al. (1996) [17] observed a difference in the number of mast cells in toluidine blue stained sections and by the immunohistochemical staining of mast cells by using monoclonal antibodies against the human mast cell proteases, tryptase and chymase. They found a decreased number of mast cells in toulidine blue stained sections. The obvious reason for this discrepancy is that only a few of the activated mast cells are detectable in toluidine blue stained sections. Maximal degranulated and resting mast cells can be stained immunohistochemically.

Joseph S. et al. (2003) in their study comparing toluidine blue and thionin noted that toluidine blue showed more intact mast cells as compared to thionine. Hence, Carnoy's fixative toluidine blue is a better stain as compared to thionin [21].

Before any definitive conclusion can be reached, additional research must be conducted at histochemical levels. Such research should make use of specific histochemical labeling techniques so that the products of expelled granules may be identified in the connective tissue and so that the decrease in the mast cell counts may be correlated to the increased concentration of the degranulation products.

Standardization of the conventional methods, strict requirement for mast cell identification, immunohistochemical staining of mast cells using antibodies raised against granule proteases, and Western blotting with specific antihuman mast cell tryptase on jaw cyst extract samples may throw more light on the role of mast cells in the pathogenesis of cysts.

Mast cell plays a contributory role in the pathogenesis of odontogenic cysts which are often treated by surgical enucleation. In extreme cases where surgical intervention is not possible, one might speculate the role of the inhibitors of mast cells or that of mast cell tryptase. In future, studies which examine the influence of mast cell antagonists on cyst pathogenesis may completely unravel the role of mast cells.

Conclusion

In the present study, more number of mast cells was noted in the subepithelial zone as compared to the intermediate and the deep zones. The number of mast cells decreased with age. No gender dependence on mast cell count was noted.

Further studies using immunohistochemical techniques of mast cells and the influence of mast cell antagonists on cyst pathogenesis may help unravel the role of mast cells in the pathogenesis of odontogenic cysts.

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