

# Mast cells and oral pathologies: A Review

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## Abstract

Mast cells (MCs) are resident cells of several types of tissues and contain many granules rich in histamine and heparin. They are distributed preferentially about the micro-vascular endothelial cells in the oral mucosa. These cells play a key role in the inflammatory process and thus their number has been found to be altered in various oral pathological conditions such as oral pyogenic granuloma, oral lichen planus, leukoplakia, oral squamous cell carcinoma, periapical cysts etc. The present review article is aimed to describe the alteration in the number of MCs along with their probable roles in these pathological conditions.

**Key words:** Mast cells, normal oral mucosa, oral pathologies

## INTRODUCTION

Mast cells (MCs) (also known as mastocytes and labrocytes) are large connective tissue cells, scattered along the capillaries and containing numerous basophilic granules in their cytoplasm, which may obscure the nucleus.<sup>[1]</sup> MC was discovered by Paul Ehrlich in 1878. He used the term “mastzellen” to describe these cells, a German term referring to feeding. Ehrlich described the association of MCs with inflammation as well as with blood vessels and neural tissue.<sup>[2]</sup> Thus, MCs are currently regarded as potent effector cells of the immune system.<sup>[3]</sup>

The role of MCs in allergic diseases, anaphylaxis, autoimmunity, reproductive disorders has been well-documented in the medical literature. However, its role in etiopathogenesis of oral pathologies is still debatable. Hence, the present review article is aimed to explore the role of MCs in initiation and progression of oral pathologies

such as oral inflammatory lesions, precancerous lesion and conditions, oral squamous cell carcinoma (OSCC) etc.

The electronic database PubMed was searched for words: MCs and pyogenic granuloma, MCs and lichen planus, MCs in normal oral mucosa (NOM), MC in periapical cyst, MCs in oral submucous fibrosis (OSMF), MCs in OSCC etc. Only highly relevant articles in English language from manual and electronic search were considered for this review article.

## MCS IN NOM

The mast cell count (MCC) in normal mucosa (NM) has been found to be 25.50/sq.mm<sup>[4]</sup> and 12.2/microscopic field at 400X using Toluidine blue stain<sup>[5]</sup> and 41.67 ± 15.38 cells/sq.mm using MC tryptase antibody.<sup>[6]</sup> MCC was found to be 71 ± 16 in normal healthy gingiva using monoclonal antibodies specific for tryptase.<sup>[7]</sup>

MCs number has been found to be altered in various oral pathological conditions. Some of the studies related to the common oral conditions are as follows:

### MCs in inflammatory reactive conditions

The MCC has been found to be raised in oral inflammatory lesions.<sup>[8]</sup> A total lack and decrease in MCC was reported in acute necrotizing and chronic marginal gingivitis

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respectively as compared to normal gingival.<sup>[9]</sup> MC density has been found to increase in gingival hyperplasia.<sup>[10]</sup>

Farahani conducted a study to compare the MCC in various reactive lesions such as irritation fibroma, inflammatory fibrous hyperplasia (IFH), peripheral giant cell granuloma (PGCG) and peripheral ossifying fibroma (POF). They found an increase in numbers of MCs in reactive lesions compared with normal gingival tissues ( $P < 0.05$ ). MCC were significantly decreased in the PGCG group compared to the IFH and POF groups ( $P < 0.05$ ). The findings of this study suggest that MCs may play some role in collagen synthesis and consequently in the variation of microscopic features of oral soft-tissue reactive lesions.<sup>[11]</sup>

### Pyogenic granuloma

Oral pyogenic granuloma is considered as a reactive process in response to etiologic factors like trauma. MCs count has been observed to be increased in connective tissue of pyogenic granuloma.<sup>[12]</sup> Murata *et al.* observed in their study that the key to wound healing after trauma is the formation of granulation tissue which seems to be controlled by various kinds of cytokines, particularly basic fibroblast growth factor (bFGF). The findings of some authors suggest that maximum amounts of bFGF are synthesized and released from some macrophages and MCs into the extracellular matrix during neovascularisation of the granulation tissue. Since its secretion is mainly through MCs, MCs may play some role in the pathogenesis of oral pyogenic granuloma.<sup>[13]</sup> Kamal *et al.* evaluated 10 cases of NOM and 30 cases of oral pyogenic granuloma for MC number using 1% toluidine blue. The average number of MCs per high field was found to be 4.58 and 10.27 in NOM and in pyogenic mucosa respectively.<sup>[14]</sup>

### Cysts of the oral cavity

MCs were found to be raised in periapical cysts and were more numerous in regions of active inflammation of periapical cysts. MCs were more common in peripheral regions and were found in close proximity to lymphocytes. These findings led authors to propose a functional relationship between these two cell populations that may facilitate elicitation of an immune response contributory to the pathogenesis of periapical lesions. The authors suggested that MCs may act as antigen presenting cells in periapical inflammatory lesions and have also been implicated in expansion of periapical cysts as it is the only cell type from which tumor necrosis factor (TNF)-alpha is immediately released from preformed stores within 10-20 min after challenge. TNF-alpha effects include stimulation of osteoclastic resorption, increase of local vascular response and promotion of chronic inflammation in human periapical lesions.<sup>[15]</sup>

Patidar *et al.* investigated the presence and distribution of MCs and compared their number in different types of radicular cysts (RC), dentigerous cysts (DC) and odontogenic keratocysts (OKC). Ten cases each of RC, DC and OKC diagnosed clinically and histopathologically were selected and stained with 1% toluidine blue. The greatest number of MCs/mm<sup>2</sup> was found in RC. The fewest MCs/mm<sup>2</sup> were found in OKC. The subepithelial zones of all cysts contained more MCs than the deeper zones.<sup>[16]</sup>

### MCs in vascular proliferations

Hagiwara *et al.* conducted a study on MC densities in six kinds of vascular proliferations which included cutaneous pyogenic granuloma, portwine stain, cavernous hemangioma, cherry angioma, Kaposi's sarcoma and malignant hemangioendothelioma using respective specimens prepared with tryptase stain. Average densities of MCs were found to be  $103.5 \pm 25.2/\text{mm}^2$  in cutaneous pyogenic granuloma,  $106.3 \pm 40.2/\text{mm}^2$  in malignant hemangioendothelioma,  $68.6 \pm 28.9/\text{mm}^2$  in portwine stain,  $105.7 \pm 56.9/\text{mm}^2$  in cavernous hemangioma,  $85.3 \pm 45.6/\text{mm}^2$  in cherry angiomas and  $82.2 \pm 28.4/\text{mm}^2$  in Kaposi's sarcoma respectively all of which were greater than that in normal skin where density was  $6.85 \pm 4.9/\text{mm}^2$ .

There were, thus, no significant differences in MC densities among those of the benign, low grade malignant and malignant types of vascular proliferations. From these results, they suggested that it seems impossible to determine whether a different MC density is responsible for different types of vascular proliferations. In addition, due to the high level of MC density in three types of vascular proliferations, they speculated that there may be a threshold level of MC density for its initiation though this hypothesis requires further clarification.<sup>[17]</sup>

### MCs in premalignant lesions and conditions

MC number was studied in normal mucosa, oral leukoplakia, OSMF, oral lichen planus (OLP) and OSCC using 1% Toluidine blue. The MC number was 25.50/sq.mm in normal mucosa, 59.50, 48.25, 59.75 and 56.75 in oral leukoplakia, OSMF, OLP and OSCC respectively.<sup>[14]</sup>

Biviji observed similar findings in leukoplakia and concluded that active agents in MCs might contribute to an inflammatory reaction seen in leukoplakia. These stimulated MCs may release interleukin-1, which causes increased epithelial proliferation that is seen in leukoplakia. Histamine may cause increased mucosal permeability which could facilitate increased access for the antigen to connective tissue.<sup>[18]</sup>

Sathyakumar *et al.* compared and correlated the mast cell density (MCD) and micro vascular density (MVD) in NM and different grades of dysplasia and to analyze their role in disease progression. MCD was assessed using anti MC tryptase and MVD was assessed immunohistochemically using anti-Factor VIII related von Willibrand factor. The mean MC and MVD for low grade dysplasia were 168.86/mm<sup>2</sup> and 142.26/mm<sup>2</sup> respectively. Similarly, for high grade dysplasia it was 193.71/mm<sup>2</sup> and 172.57/mm<sup>2</sup> and whereas, for control sections, the mean MC and MVD were 114.40/mm<sup>2</sup> and 70.80/mm<sup>2</sup> respectively. Thus, the author concluded that the number of MCs and microvessel can be used as indicators of disease progression.<sup>[19]</sup>

Studies on MCs have also been conducted by Bhatt *et al.* who noted abundant MCs i.e., 4.5 and 4.9 in OSMF respectively compared to 1.02 in normal buccal mucosa. The authors attributed vesicle formation and symptoms of itching sensation to histamine released from the MCs and suggested the concept of histamine MC chain. The MC hyperplasia could attribute to some of the signs and symptoms of OSMF.<sup>[20]</sup>

MC mediators like prostaglandins and leukotrienes are potent secretagogues for the serous and mucous cells. This could attribute to increased salivation seen in OSMF. The effect of chemical mediators can explain the histopathological changes seen in OSMF. Histamine could probably attribute to submucosal edema seen in early stages of OSMF. Due to increased vasopermeability eosinophilic chemotactic factor is released from the MCs. This could probably attribute to the eosinophils that are sometimes a part of the inflammatory cell infiltrate seen in the early stages of OSMF. Interleukin-1 from the MCs could cause increased fibroblastic response and MC derived tryptase causes increased production of type-1 collagen and fibronectin thereby attributing to increased fibrosis.<sup>[20]</sup>

Sabarinath *et al.* evaluated the MCD and MVD in NM and in different grades of OSMF. The results showed a significant increase in MCD and MVD among OSMF cases. Moreover, a positive correlation was found between MCD and MVD.<sup>[21]</sup>

Jontell *et al.* observed that MC number was elevated in OLP in comparison to healthy oral mucosa.<sup>[22]</sup> Zhao *et al.* proposed that MCs play an important role in the pathogenesis of OLP. The interactions between MCs and T-cells, which are related to the disease process are relevant to both the initiation, vaso-induction and effector phases of OLP. They observed a MCC of 151.5/sq.mm in lichen planus. They considered MC as the offender in the basement membrane destruction. TNF-alpha released from MCs

causes increased synthesis of matrix metalloproteinases like collagenase, which cause the basement membrane destruction and causes increased expression of adhesion molecules like E-selectin and ICAM. This could probably cause increased leukocytic migration.<sup>[23]</sup>

Histamine causes vasopermeability leading to submucosal edema and antigen induced T-cell proliferation. This could attribute for the characteristic trafficking of lymphocytes. The cytotoxic lymphocytes, thus recruited by MCs cause the basal cell degeneration, keratinocyte apoptosis and thus characteristic civatte bodies seen in OLP.<sup>[23]</sup>

Sharma *et al.* found an increase in MCC in OLP and oral lichenoid reaction (OLR) in comparison to NOM. However, no significant differences in MCC were noted between OLP and OLR.<sup>[24]</sup>

### Salivary gland tumors

Vidal *et al.* investigated the density of MCs and microvessels in minor salivary gland tumors. 41 cases of minor salivary gland tumors (pleomorphic adenoma,  $n = 10$ ; adenoid cystic carcinoma,  $n = 11$ ; mucoepidermoid carcinoma,  $n = 10$ ; and polymorphous low-grade adenocarcinoma) were investigated using immunohistochemistry for MC tryptase and von-Willebrand factor. Density of MCs was higher in mucoepidermoid carcinoma; however, no differences in the number of these cells were observed between the different types of tumors ( $P > 0.05$ ). The number of MCs was higher in periparenchymal areas in all tumors, but the difference was not significant ( $P > 0.05$ ). Mucoepidermoid carcinoma showed the largest number of periparenchymal MCs, whereas pleomorphic adenomas showed the smallest number of intraparenchymal MCs ( $P > 0.05$ ).<sup>[25]</sup>

The highest micro-vessel density (MVD) was observed in mucoepidermoid carcinomas, being this difference statistically significant when mucoepidermoid carcinoma was compared to pleomorphic adenoma ( $P = 0.0034$ ) and polymorphous low-grade adenocarcinoma ( $P = 0.004$ ). MVD was significantly higher in adenoid cystic carcinoma.<sup>[25]</sup>

### MCs in squamous cell carcinomas

Rojas *et al.* observed that MC numbers were increased in lip squamous cell carcinoma (LSCC).<sup>[26]</sup> Iamaroon *et al.* observed that MC numbers were increased in OSCC compared to NM using anti tryptase antibody. A significant correlation between the MC and microvascular counts in oral SCC as well as a linear increase in the number of MCs and progression of SCC was also observed. The authors suggested that MCs may upregulate angiogenesis in oral SCC carcinogenesis, perhaps via the release of MC tryptase.

Hence, numbers of MCs may be used as indicators of disease progression.<sup>[6]</sup>

Jahanshahi *et al.* in their retrospective analytical study, found a significant correlation between MVD and MCD in NOM ( $P < 0.001$ ), but in spite of a higher density of MCs and microvessel observed in OSCC compared with NM there was no significant correlation between them ( $P = 0.731$ ).<sup>[27]</sup>

Gomes *et al.* studied the number of MCs in 4 groups: NOM ( $n = 6$ ); mild dysplasia in actinic cheilitis (MDAC) ( $n = 13$ ); severe dysplasia in actinic cheilitis (SDAC) ( $n = 13$ ); and LSCC ( $n = 15$ ). The largest mean number of MCs per group was observed in LSCC (40.1), followed by MDAC (30.5), SDAC (28.6) and NOM (12.2). There were significant differences between NOM and MDAC ( $P < 0.05$ ) and between NOM and LSCC ( $P < 0.05$ ). The increased density of MCs observed in AC and in LSCC compared to NOM suggests a role of the MCs in the development of these lesions.<sup>[5]</sup>

Mohtasham *et al.* compared the MCC and MVD among NOM, oral dysplastic epithelium and low- and high-grade OSCC. The mean MCC and MVD, as well as the correlation between them, were evaluated by immunohistochemical staining. The results showed a statistically significant increases in mean MCC and MVD between NOM and epithelial dysplasia, NOM and OSCC and epithelial dysplasia and OSCC ( $P < 0.05$ ), but there were no statistically significant differences in MCC and MVD between low- and high-grade OSCC. This significant between MCC and MVD is in agreement with the idea that MCs promote tumor progression via up-regulation of angiogenesis.<sup>[28]</sup>

The results of a recent study suggested that angiogenesis occur in OSCC and might be used as an index to express the aggression of the disease however MCs make up only a part of the complex process of angiogenesis along with other factors secreted by tumor.<sup>[29]</sup> In 2007, A study reported a decrease in MCs count in specimens of OSCC and premalignant oral hyperkeratosis (leukoplakia). This decrease in number of MCs might be related to the migration failure of these cells, possibly reflecting an important modification in the microenvironment during tumor initiation and progression.<sup>[30]</sup>

### MCs in immunological disorders

MC numbers were increased in recurrent aphthous ulcers and local MCs showed signs of activation or degranulation suggesting active involvement of this cell type in recurrent aphthous ulcer pathogenesis.<sup>[9]</sup>

## CONCLUSION

From the results of these research works, it may be concluded that though acting as defense cells under normal conditions, they may also help in disease progression. Further research studies on mast cells may enhance our knowledge on their role in pathogenesis of various oral pathologies.

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