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Original Research Article

Quantitative and qualitative assessment of mast cells in oral lichen planus to implicate its role in pathogenesis

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Abstract

Aim: To assess mast cells both quantitatively and qualitatively using light and electron microscopes in order to ascertain their possible involvement in the pathophysiology of oral lichen planus.
Materials and Methods: Five healthy controls and thirty lichen planus patients were included. Toluidine blue and uranyl acetate staining were used to examine tissue sections under light and electron microscope.
Results: Sections stained with toluidine blue showed that there were more mast cells in the reticular region than in the juxtaepithelial zone. Degranulated mast cells were discovered near lymphocytes under an electron microscope.
Statistical analysis: The distribution of mast cells in the various lichen planus zones and control groups was statistically examined using the Mann-Whitney U and t tests.
Conclusion: The immunopathogenesis of lichen planus may be significantly influenced by molecular interactions between mast cells and lymphocytes, as evidenced by the significant increase in mast cell numbers in the reticular region and their close connection with lymphocytes.

Keywords: Lichen planus, Mast cells, Toluidine blue

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1. Introduction

A mucocutaneous condition with an unclear etiology, lichen planus is typified by keratotic plaques on the skin and occasionally in the mouth cavity.[1] It manifests itself in various clinical forms, and according to World Health Organization, it is considered as a precancerous condition.[2] Histopathologically, presence of hyperkeratosis, degeneration of basal cells, thickening of basal lamina and infiltration of lymphocytes is evident in juxtaposition to epithelial layer.[1] Mast cells are traditionally considered as elements of connective tissue, and because they contain biologically active chemicals including heparin, histamine, and proteolytic enzymes, they contribute to the pathophysiology of certain tissue responses. Mast cells are varied in size possessing 50–100 granules, a diameter of roughly 12 µm, and a life period of weeks to months.[3] Through the induction of endothelial–leukocyte adhesion molecules, mast cell granules containing the tumor necrosis factor-alpha and other proinflammatory cytokines promote leukocyte infiltration during inflammation in a variety of diseases, including periapical inflammation, gingivitis, pulpitis, and lichen planus.[4]

In oral lichen planus (OLP), 60% of mast cells are degranulated compared to 20% in normal buccal mucosa.[5] Chymase, a mast cell protease, is a well-known activator of MMP-9, which directly or indirectly impacts the basement membrane alteration in OLP by inducing T-cell-derived MMP-9.[6] Therefore, it can be said that mast cells may have an essential role in compromising of basement membrane in OLP.

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Diagnosis of disease may be done under light microscopy but it contributes slight to the understanding of etiopathogenesis or the exact nature of tissue variation. The ultrastructure of the epithelial–connective tissue junction in OLP reveals a variety of changes from the normal.[7]

Under a light microscope, mast cell secretory granules exhibit a characteristic metachromatic staining pattern with toluidine blue. Sections stained with toluidine blue histologically appear to have rounded mast cells, however transmission electron microscopy or immunohistochemistry may show a more stellate or dendritic appearance.

Mast cells of healthy oral mucosa seen under Electron microscopy shows homogeneous and condensed granules in the lamina propria. The portion of the lamina propria not infiltrated by lichen planus showed fully granulated mast cells. Altered ultrastructural morphology was evident in the deeper portion of the subepithelial region. Mast cells, at any time in normal tissues, never present an altered morphology of their granules.[8]

Mast cells have been seen in OLP lesions in multiple investigations, but little is known regarding their location or pathophysiological function.[9] Thus, present study was undertaken to evaluate mast cells under the light microscope in addition to electron microscope and to evaluate the mast cells population both qualitatively and quantitatively.

2. Materials and Methods

Thirty patients of mean age 35.5 years with OLP together with five healthy controls (mean age 45.5 years) were recruited for the study. Based on clinical and histopathological criteria in accordance with the WHO recommendation, diagnosis of OLP was established. Administration of local anesthesia was used to obtain biopsy specimens including either diseased or healthy buccal mucosa. Each biopsy was divided into two portions, one for light and one for electron microscopy. The portions for light microscopy was fixed in 10% formal saline, paraffin sections were prepared and stained with hematoxylin and eosin (H and E) and toluidine blue. The H & E stained sections were used for the histopathological diagnosis and toluidine blue slides to evaluate the mast cell. The sections were examined under 40× and photomicrographs were taken. Each photomicrograph was divided into 5 × 5 grids using image analyzer software and mast cells per block were counted. For electron microscopic examination, 2.5% glutaraldehyde and 2% paraformaldehyde was used as fixative for other half of the section. Ultrathin sections were taken using ultramicrotome. Uranyl acetate and lead citrate were used to stain the section which was further examined under Morgagni (Fie Company) Transmission electron microscope. Each case was studied in five different fields, which were again subdivided as different areas using copper grids selected. Mast cells were qualitatively evaluated by looking at their morphology, granule size and shape, and different cellular connections with neighboring cells.

3. Results

Mast cells were visible under optical microscopy in slices of the OLP lesions stained with toluidine blue in the reticular and juxtaepithelial regions [**Figure 1**, **Figure 2**]. Their metachromatically pigmented granules served as their distinguishing feature.

Mast cell distribution per block of grid was compared between juxtaepithelial region and reticular region of lichen planus and control group using *t* test. Statistically significant difference was noted in lichen planus but in case of control group, the results came out to be nonsignificant [**Table 1**].

This study compared mast cell distribution within various zones of lichen planus with their respective zones of control group by means of Mann–Whitney U test. Both the zones of lichen planus and control group showed statistically significant difference. [**Table 2**].

Under transmission electron microscopy, the connective tissue of OLP showed the existence of lymphocytes with small- and medium-sized nuclei folded and centrally placed. Presence of Plasma cells, Langerhans cells and mast cells was detected in the connective tissue. Presence of membrane-bound secretory granules occupying a large part of cytoplasm was indicative of mast cell. Mast cells were identified on the basis of the presence of many granules and a few of which appeared electron-lucent due to the process of degranulation. Mast cells were either partially degranulated with the extension of the villous process being evident or completely degranulated having lost the nucleus. Lymphocytes were seen in contact with macrophages and mast cells at high frequency per field view [**Figure 3**, **Figure 4**].

Table 1: Distribution of mast cells in juxtaepithelial and reticular region of lichen planus and control group

	Mean no. of mast cells/block of grid ± standard deviation		**Mean difference**	***t* Value**	***P* value**
	Juxtaepithelial	Reticular			
Lichen planus	1.043±0.504	1.755±0.710	−0.712±0.392	−9.941	<0.05 (significant)
Control	0.160±0.167	0.680±0.641	−0.52±0.576	−2.018	0.114 (non-significant)

Table 2: Comparison between lichen planus and control group with respect to juxtaepithelial and reticular region

Mean no. of mast cells/block of grid	Zones of connective tissue	Lichen planus	Control	Mann–Whitney *U* test	*P* value
	Juxtaepithelial	1.043±0.504	0.160±0.167	7.50	0.001 (sig.)
	Reticular	1.755±0.710	0.680±0.641	19.0	0.006 (sig.)

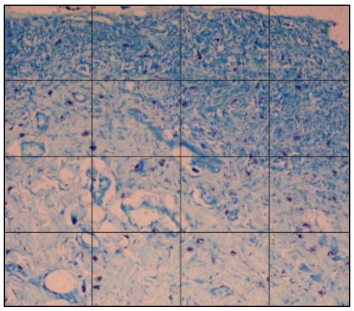

Figure 1: Photomicrograph showing mast cells predominant around blood vessels (toluidine blue, ×40).

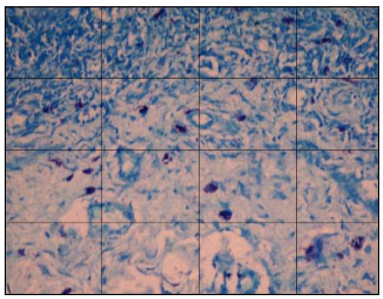

Figure 2: Photomicrograph showing large number of mast cells in the reticular area (toluidine blue, ×40).

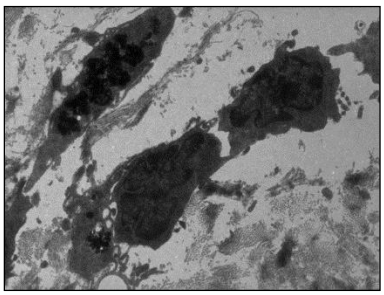

Figure 3: Electron micrograph of the lichen planus showing mast cell in close association of lymphocyte (×1400).

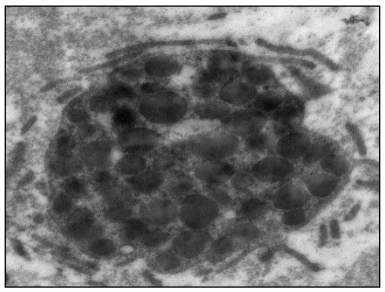

Figure 4: Electron micrograph showing activated and partially degranulated mast cell showing both electron dense and electron lucent granules (×1000).

4. Discussion

A chronic idiopathic immune-mediated inflammatory condition is suggestive of Lichen Planus (LP). The precise etiopathogenesis of OLP is unknown.[10] Plasmacytoid dendritic cells, mast cells alongwith population of T cells, contribute in a multifaceted interplay to bring about the inflammatory cascade, destroying the basal keratinocyte.[11]

Traditionally mast cells have been considered constituents of connective tissue with metachromatic granulated cytoplasm, the metachromasia which under normal conditions being metachromatic.[12] Higher mast cell numbers as a constant finding in the lesion of OLP brought it under further investigation concerning the involvement of mast cells and mediators that they might contribute to the phenomenon of chronic inflammation, with relevance also to the functional role that the mast cell- immunocompetent cell interactions might play in the context of OLP.[13]

Mast cells play an active role in OLP by the action of their mediators on endothelial cells which was indicated by the prevalence of connective tissue-type mast cells during development of the lesion. Vasoactive amines and enzymes, which induce vasodilation and increased vascular permeability are the mast cell mediators that get released rapidly at the time of degranulation.[14,15]

These mediators also have strong immunoregulatory effects on various cell types, while several cytokines produced by T lymphocytes impact mast cell migration and the release of mediators. Mast cell proteases could play a role in changes to basement membranes during inflammation in the oral cavity, such as those that facilitate the entry of cytotoxic lymphocytes into the epithelium in OLP.

Former studies done under light microscopy have suggested that intraepithelial locations can also occasionally include mast cells. Electron microscopy has recently demonstrated this, confirming that mast cells are present within a variety of epithelia, including normal, inflamed human gingival epithelium, diseased human renal epithelium and human epidermis affected with alopecia mucinosa.[16]

In our study, when the mean cell count was compared between normal mucosa and lesion of OLP it was found out that the reticular and juxtaepithelial regions of OLP had an average of more mast cells than normal oral mucosa. This stayed in line with other research done by various authors.[13]

The mast cell population was noticed to be concentrated near the endothelium-lined blood channels.

Compared to the juxtaepithelial region, the reticular region's mast cells were more degranulated, which would suggest a role for mast cells in the pathogenesis of lichen planus. Additional data suggests that mast cells and altered mast cells are important in the pathophysiology of OLP. Mast cell morphological changes were closely associated with the disease's chronicity.

Jontell et al. demonstrated the existence of mast cells with altered morphology in OLP lesions. Granules in mast cells which were affected varied from nearly homogeneous osmiophilia to granules comprising coarse-grained material. Granules fused together and modified granules were extruded into the extracellular space. Mast cells in sensitized tissue released vasoactive amines, which act on the endothelial cells, resulting in increased permeability.[16] In the existing study, active mast cells stayed evident in the close proximity to lymphocytes. Recruitment of these cells from the blood stream may be attributed to the local proliferation of lymphocytes. As a result of the recruitment, it is possible that the mast cells participate since they have the capacity to influence permeability of endothelium.

The current observation supports the role of mast cells in recruiting T lymphocytes to the subepithelial infiltrate of the OLP lesions, given the morphological changes observed in mast cells and their role in hypersensitivity.[17]

The analysis of the data suggests that mast cells may play a role in the oral lichen planus (OLP) epithelial basement membrane disruption, which permits lymphocytes to pass through the damaged basement membrane and enter the OLP epithelium. Therefore, mast cell protease may either directly or indirectly aid in the rupture of the basement membrane in OLP by activating T-cell-secreted MMP-9.[15]

It is evident that there are now more mast cells in the connective tissue of OLP. The reticular region showed a greater density of mast cells than the juxtaepithelial region, indicating an innate mechanism in the recruitment of mast cells and their role in the pathophysiology of OLP.

Degranulating mast cells were shown closely interacting with lymphocytes under an electron microscope. This supports the idea that in the endogenously guided pathophysiology of OLP, mast cells are essential.

5. Conclusion

Many concerns about its pathophysiology and origin remain unresolved. The current study found that the reticular region had a markedly higher number of mast cells, most of which were seen to be intimately related to lymphocytes. Consequently, the relationship between mast cells and lymphocytes can be definitely implicated to explain immunopathogenesis of lichen planus.

6. Sources of Funding

None.

7. Conflict of Interest

None.

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