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The compare number of mast cells in biopsy specimens of patients with erosive & non- erosive lichen planus

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A B S T R A C T

Lichen planus (LP) is a common disease of the skin and/or mucous membranes which usually affects the oral mucosa. The oral LP could appear in two forms: erosive and non-erosive OLP. Furthermore the immune cells infiltration is observed in the intermediate epithelium and connective tissue of LP patients. The aim of this study was to compare the frequency of mast cells presence in the erosive and non-erosive LP. The study sample size was included the 26 erosive LP cases, the 26 non-erosive LP cases and 5 control cases. The paraffin blocks was sectioned at 5 μ m tick and stained with the Toluidine Blue. The data were analyzed with the descriptive statistics and the one-way Analysis of Variance (ANOVA) using SPSS.15. The mean numbers of the mast-cells were respectively 5.9 ± 7.1 , 2.5 ± 3.1 and 0.3 ± 1.8 in erosive LP cases, non-erosive LP cases and the control group. The increased number of mast cells in the clinical types of oral LP represents the definitive role of these cells in the pathogenesis of oral LP. These cells probably play a main role in the recruitment of lymphocytes into the sub-epithelial zone. In addition, the significant increase in the number of mast cells in erosive LP compared with non-erosive LP could represent a further possible role of mast cells in the malignant potential of these clinical types of oral LP.

Introduction

LP is a chronic and relatively common skin-mucosal disease which caught oral mucosa (1). Nevertheless the etiology of LP is unclear, severe infiltration of CD8 and CD4 cells has been observed in LP lesions which are localized in the epithelium and connective tissue interface (2). Low accumulation of immunoglobulin and

complement is seen in lesions (2). Basically there are two types of oral lesions including atrophic and reticular types (1).

Reticular LP is greater in prevalence than the erosive type. This type of LP usually does not create symptoms or signs and

involved in the posterior buccal mucosa in a two-sided manner (1).

Atrophic LP prevalence is not as much as reticular type, however they have more importance for patients because these lesions are accompanied by signs (1).

To some researchers, there exist higher risk of carcinogens in atrophic LP epithelium (1) and if malignancies happen, it is more likely associated with atrophic type of LP (1, 2).

Mast cells are large granular cells deriving from CD34⁺ stem cells of bone marrow which are distributed in the connective tissue in normal state (3).

Granules contain a number of precursor mediators. These mediators are secreted following degranulation of Mast cells having stimulatory, inhibitory or toxic on the other cells (4).

Degranulation ability of Mast cells in response to various stimuli including drugs and chemicals is a basic characteristic of their biological activity (5) Studies on the role of Mast cells in normal and Pathologic conditions have shown that Mast cells are complicated and well organized cells with multiple functions playing a central role in intrinsic and acquired immunity (3). Recently some investigations have been performed about the role of Mast cells in oral LP.

Ramesh and Janardhanan expressed in a study about the density of Mast cells in oral LP that the increased Mast cells density is seen in oral LP compared to normal mucosa which is indicative of special role of Mast cells in different phases of LP (6).

Moreover, in a research by Jose et al it was observed that the number of Mast cells was higher in LP and lichenoid lesions than normal mucosa (7).

In the study of Sharma et al, a significant increase in the total number of Mast cells was observed in oral LP and oral lichenoid lesions in comparison to than normal mucosa of the mouth (3).

Jahanshiri et al (2012) concluded that there was no difference in terms of overall number of Mast cells in oral LP and oral lichenoid lesions (8).

On the other hand, the possible role of Mast cells as angiogenic stimulator in tumors is approved. Mast cells induce new vessel formation through releasing angiogenic factors. Mast cells accumulation leads to the growth and invasion of a large number of malignancies (9).

Mohtasham et al suggested in their study that there exist an increased number of Mast cells and new vessels in dysplastic epithelium and oral SCC compared to normal mucosa of the mouth since angiogenesis causes progression and metastasis of malignant tumors (10).

In addition, involvement of mast cells in several other types of malignancy including carcinoma of breasts (11), stomach (12), esophagus (13), oral cavity (14), lungs (15), larynx (16), and melanoma (17).

According to the recent findings on the possible role of mast cells in the pathogens of oral LP and SCC and according to the different between the potential of malignancy of erosive and non-erosive oral LP, in this study it was tried to draw a comparison for the first time between the

numbers of mast cells in erosive and non-erosive oral LPs.

The aim of this study was to compare the number of mast cells in erosive and non-erosive oral LP.

Material and Methods

In a cross-sectional descriptive-analytic study, which was performed in the Department of Oral Pathology of the Faculty of Dentistry of Tabriz University on patients with LP, the number of mast cells involved in erosive and no-erosive oral LP was studied.

Inclusion Criteria

- 1- Definitive diagnosis of LP using criteria proposed by WHO (18) (Table 1)
- 2- Presence of epithelium and adequate connective tissues for examination of research samples
- 3- The patient shall not consume other drugs or other treatments for other diseases.

Table 1

Criteria proposed by WHO includes 3 parts:
Clinical criteria
Histopathological criteria
Criteria analysis and final diagnosis

Exclusion Criteria

- 1- Lesions with similar histopathological demonstrations such as lichenoid reactions
- 2- Lack of adequate tissues for counting and studying cells
- 3- Defective clinical information in files

Implementation Method

LP samples were obtained from the archive of the pathology department of the Faculty of Dentistry of Tabriz University of Medical Sciences. The type of LP (erosive and non-erosive) was diagnosed by two oral pathologists on the basis of clinical information and findings observed in histopathological samples stained with Hematoxylin and Eosin. The assessments were based on the criteria introduced by WHO.

Samples included 26 erosive LP and 26 non-erosive LP patients as well as 5 participants with normal mucosa. The aforementioned samples formed the control group. Tissue sections with thickness of 5 μ m were cut from paraffin blocks and were stained with Blue Toluidine.

The number of mast cells was counted in the lams associated with each tissue sample and the mean number of mast cells was calculated as well.

Moral Considerations

Since no therapeutic intervention was made in this study, there was no specific moral consideration. In addition, all of the moral considerations in relation to the files and documents of patients were taken into account.

Result and Discussion

In this study, 52 patients with lichen planus/LP (26 with erosive LP and 26 with non-erosive LP) and 5 control samples were studied.

The age of patients varied between 22 and 84 years and the mean age was 42 years and 54.8% of patients were male and 45.2% of patients were female.

In samples colored with blue Toluidine, mast cells were mainly observed below the band like infiltration of lymphocytes in the reticular layer of connective tissues. Mast cells were clearly countable with metachromatic granules in study samples. In all erosive LP samples (100%) as well as 23 (88.5%) of the 26 non-erosive LP samples, mast cells were observed.

The mean number of mast cells in the oral erosive LP samples was 7.1, falling in the 1-19.6 range (Diagram I) (Figure I).

The mean number of mast cells in the non-erosive samples with oral lichen planus was 3.1, falling in the 0.3-9.3 range (Diagram II) (Figure II).

Analysis of the control group, which included biopsied samples of mucous membrane of wisdom teeth, the mean number of mast cells in healthy mucous membranes was 1.8, falling in the 1.8-2.1 range (Diagram III) (Figure III).

The mean number of mast cells in erosive LP samples was significantly higher than that of non-erosive and normal tissue sample ($P < 0.01$) (Table I).

In addition, the Scheffe follow-up test revealed that the mean number of mast cells in the erosive group was significantly higher than that of the non-erosive group and the group with healthy mucous membrane ($p < 0.01$). The mean number of mast cells in the non-erosive group was also significantly higher than that of the healthy mucous membrane group ($P < 0.05$).

Oral LP (lichen planus) is a relatively common and chronic oral disease that mainly affects oral mucous membranes (1). It is considered an immunologic disease which, at the microscopic level, is similar to

an increased sensitivity reaction with the intervention of T-cells (19). Factors such as stress, diabetes, type C hepatitis, trauma, and increased sensitivity to medicine and metals can be considered the co-factors contributing to the development of LP (20). The majority of patients suffering from LP are adults and the elderly. The ratio of development of this disease in women and men is 3 to 2 and thus women are involved more than men. Prevalence of oral LP is reported to be between 0.1 to 2.2%. Although the cause of this disease is unknown, degeneration of basal cells is the histopathological cause of this disease. Oral LP has different clinical demonstrations but it is mainly manifested in erosive and non-erosive forms and its reticular form is more common as well. This disease is diagnosed with hyperkeratosis, degeneration of basal cells, thickening of the base membrane, and concentration of submucosa lymphocytes (1, 19).

Mast cells are important immune cells containing Secretory granules. These cells are generally located in the endothelium of small vessels of oral mucus and dental pulps. They contain factors whose release leads to an increase in the concentration of leukocytes in inflammatory reactions caused with different diseases. Mast cell proteases may play a role in changes of the base membrane in the inflammation of the oral cavity (21-22).

Studies have been performed to examine the role of mast cells in the development of oral LP. Some of the studies have reported an increase in the number of mast cell as a result of oral L (2, 6, and 8).

However, few studies have compared the frequency of mast cell in clinical erosive and non-erosive LP types.

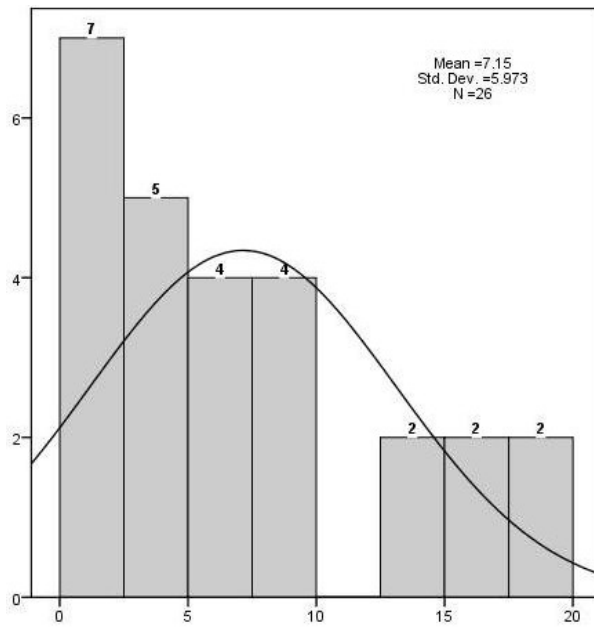


Figure.1 Distribution of mast cells in samples with oral erosive LP

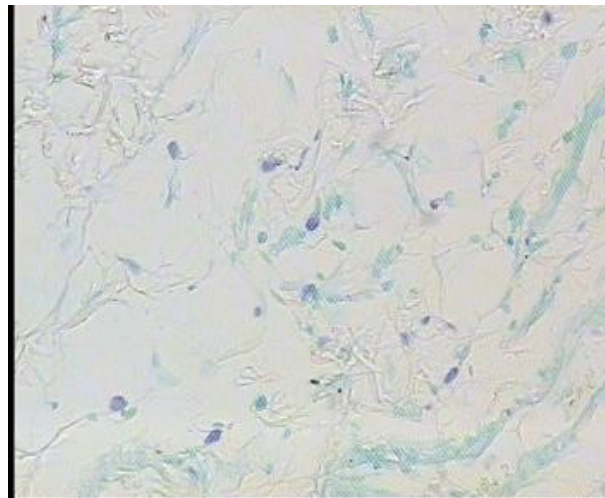


Diagram.I Erosive LP sample stained with the Toluidine Blue (magnification $\times 40$)

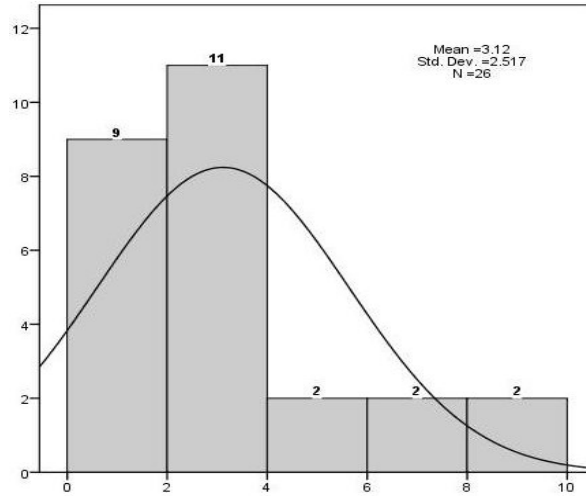


Figure.II Distribution of mast cells in samples with oral non-erosive LP

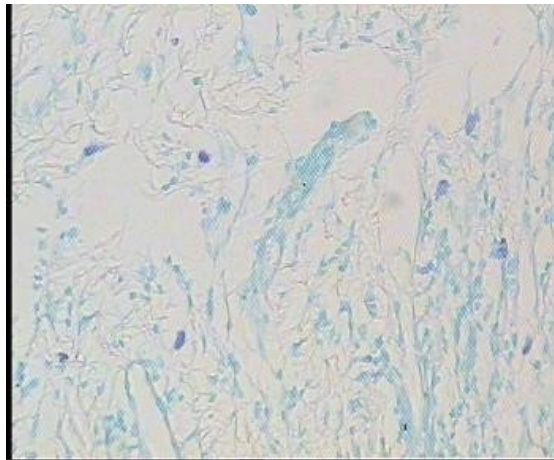


Diagram.II Non-erosive LP sample stained with the Toluidine Blue (magnification $\times 40$)

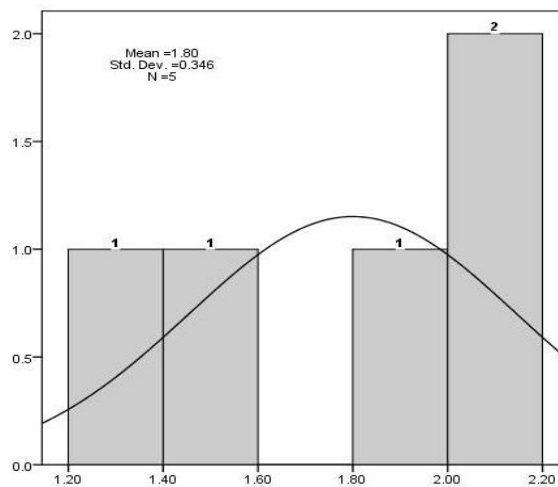


Figure.III Distribution of mast cells in samples with normal mucosa

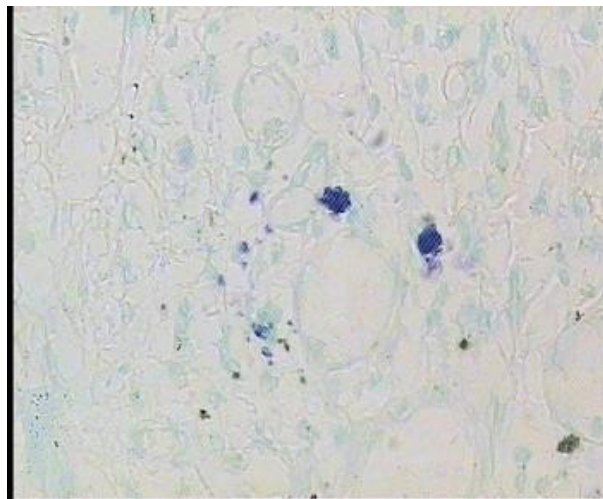


Diagram.III Normal mucosa sample stained with the Toluidine Blue (magnification $\times 40$)

Table.I The ANOVA for the numbers of mast cells involve in the erosive and non-erosive LP groups and normal mucosa.

		Count	Mean \pm Std Deviation	Range	P
Mast Cell	Erosive LP	26	7.14 \pm 5.97	1-19.6	0.002
	Non-erosive LP	26	3.11 \pm 2.51	0.30-9.30	
	Normal Mucosa	5	1.80 \pm 0.34	1.30=2.10	

In the present study, the number of mast cells in erosive and non-erosive oral LP cases was examined and compared.

In this study, an increase was observed in the number of mast cell in the erosive and non-erosive types of oral LP as compared to the number of mast cells in normal mucus, which reflected the significance of presence of mast cells in the pathogenesis of oral LP. This finding complies with the findings of the following studies (6, 22-27).

In the study conducted by Janardhanan and colleagues, the prevalence of Mast Cells in patients with oral LP was examined and it was expressed that the Mast Cells frequency in the mucosa of the patients with oral LP is significantly higher than those with normal mucosa (6).

Amberkar and et al study showed that the numbers of Mast Cells in patients with oral LP were significantly more than those in normal mucosa (23) which was consistent with our results.

In a study conducted by Jahanshahi and colleagues on 52 cases of oral LP, there was a significant difference in the number of Mast Cells observed in oral LP and lichenoid lesions compared to the normal mucosa (22).

Moshref and colleagues stated that the mean of Mast Cells was respectively 38.4 and 3.57 in oral LP and normal samples which was significantly higher in patients with oral LP (24).

In a study conducted by Jontell et al, the frequency of Mast Cells in oral LP and normal mucosa was compared and consequently the further presence of Mast Cells was observed in LP (25).

Nafarzadeh and colleagues compared the 34 cases of oral LP with 26 cases of oral lichenoid and they demonstrated that the total number of Mast Cells was significantly higher than in the oral LP group compared to the oral lichenoid lesions and controls (26). Hall et al observed the presence of the Mast Cells in oral LP (27). In the present study, the density of Mast Cells was higher under the inflammatory cells infiltration which is consistent with the research findings of Janardhanan, Jahanshahi, Jose and Bhatt.

The distribution of Mast Cells has been significantly increased beneath the inflammatory band in the study conducted by Janardhanan et al, so they believed that Mast Cells distribution in the different levels could indicate their roles at different stages of oral LP. The first phase may include dilated veins instead of blood vessel and lymphocytes could enter through these vessels within the tissue. Consequently, the lymphocytes would bind to the sub-epithelial region and the Mast Cells might also release cytokines that cause some degradation of the extracellular matrix which leads to propel the target lymphocytes towards the basement membrane (6). Jose and colleagues studied on patients diagnosed with oral LP and they found that the number of Mast Cells has more increased in the deep connective tissue compared to the underlying connective tissue which is located under the epithelium (7).

Bhatt and colleagues propounded the Mast Cells as a group of connective tissue cells with dense cytoplasm filled with granules

beneath the sub-mucosa especially around the vessels (28).

Furthermore, in a study conducted by Juneja et al, it was indicated that the number of Mast Cells was increased in the degenerated zone of basement membrane (29).

Zhao et al indicated that the 20% of Mast Cells are in the normal basement membrane and the 60 % of Mast Cells are located in those connective tissues zones of oral LP, where the basement membrane is damaged. They stated that T cells in oral LP generate and secrete the RANTES which could induce the de-granulation of the Mast Cells in the oral LP (30).

The malignant potential risk of LP is still discussed (especially erosive LP). Some researchers believe that atrophic epithelium in patients with LP, are more susceptible to carcinogen factors, thus the risk of malignancy is higher in these patients (1).

In a study conducted by Mardani and colleagues, they observed the malignant transformations in three women and one man after evaluating the 386 LP cases and following them up during three years. They reported all malignant transformations including all type of erythema, atrophic LP. Their results confirm the hypothesis of an increased risk of malignant transformation of oral LP (31).

Barnard and colleagues researched on the 241 patients diagnosed with OLP during ten years. The results of studies indicate that the malignant transformations were detected in 9 cases. It should be noted that the most of which were associated with atrophic or erosive LP and the tongue transformation were found in 6 out of the 9 cases. These results confirm the malignant potential risk of LP (32).

The Mast Cells interventions have been followed in several types of malignancy such as breast cancer (11), gastric cancer (12), esophageal cancer (13), oral cavity cancer (14), lung cancer (15), larynx cancer (16) and melanoma (17).

It has been reported that there are the increased numbers of Mast Cells in malignant tumors such as lung carcinoma and esophageal SCC (esophageal squamous cell carcinoma) (33).

In a study conducted by Mohtasham et al, after evaluating the 42 patients diagnosed with oral SCC, 22 cases with dysplastic oral mucosa and 6 cases with normal mucosa, they reported that the increased number of Mast Cells has significant relationship with the normal mucosa transforming into the dysplasia and oral SCC.

There was a significant increase in the mean number of Mast Cells and the frequency of capillaries in the dysplastic epithelium and oral SCC compared with the normal mucosa. The researchers concluded that this strong relationship between the Mast Cells frequency and the abundance of capillaries could be a definite reason in order to the Mast Cells influence on the tumor genesis via angiogenesis. This means that the formation of new blood vessels would lead to the invasion and metastasis of malignant tumors (13).

In the present study, the comparison between the erosive and non-erosive groups of oral LP demonstrated that the number of Mast Cells in erosive LP cases is significantly more than the non-erosive LP ones.

Furthermore, in a study which was consistent with our present research we observed that the Mast Cells frequency has

been examined in the various type of clinical erosive and non-erosive LP.

In a study conducted by Amberkar and colleagues, 40 patients diagnosed with oral LP (20 cases with erosive LP and 20 cases with non-erosive LP) and 20 normal cases were examined and it was concluded that the number of Mast Cells in erosive LP is significantly more than its frequency in the reticular lesions and normal group which is consistent with our results (23).

Conclusion

Increasing the number of Mast Cells in the clinical types of oral LP suggests a definite role of these cells in the pathogenesis of oral LP. These cells probably propel the lymphocytes towards the sub-epithelial zone. The significant increase in the number of Mast Cells In the erosive LP compared with non-erosive LP might indicate a possible role of these cells in the increasing of the malignant potential in this clinical oral LP type.

Recommendation

- 1) Evaluating the angiogenic factors and the densities of Mast Cells in the various types of the erosive and non-erosive LP.
- 2) Examining the presence of Mast Cells in premalignant lesions.
- 3) Researching the densities of Mast Cells in the various layers of the erosive and non-erosive lesions.

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