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Original Research Article

Comparative Histopathological Analysis of Inflammatory Cell Infiltrate Patterns in Chronic Oral Mucosal Lesions

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Abstract

Background: Chronic oral mucosal lesions represent a diverse group of pathological conditions characterized by persistent inflammatory responses. Understanding the specific patterns of inflammatory cell infiltration is crucial for accurate diagnosis, prognostication, and treatment planning. This study aimed to compare the histopathological patterns of inflammatory cell infiltrates across different chronic oral mucosal lesions.

Methods: This cross-sectional analytical study examined 180 biopsy specimens from patients diagnosed with oral lichen planus (OLP, n=60), oral leukoplakia (OL, n=45), chronic hyperplastic candidiasis (CHC, n=35), and oral submucous fibrosis (OSMF, n=40). Histopathological analysis was performed using hematoxylin and eosin staining, with immunohistochemical markers (CD3, CD20, CD68, and mast cell tryptase) employed for inflammatory cell characterization. Quantitative analysis of inflammatory infiltrate density, distribution patterns, and cellular composition was conducted.

Results: Oral lichen planus demonstrated significantly higher lymphocytic infiltration (78.4 ± 12.3 cells/HPF) compared to other lesions ($p<0.001$). Band-like subepithelial infiltration was predominant in OLP (91.7%), while diffuse patterns characterized OSMF (72.5%). CD3+ T-lymphocytes constituted the majority of infiltrates in OLP (68.2 ± 8.7%), whereas CD68+ macrophages were significantly elevated in CHC (42.3 ± 9.1%, $p=0.003$). Mast cell density was highest in OSMF (18.6 ± 4.2 cells/HPF) compared to other groups ($p<0.001$).

Conclusion: Distinct inflammatory cell infiltrate patterns exist among chronic oral mucosal lesions, providing valuable diagnostic markers and insights into disease pathogenesis. These findings support the implementation of immunohistochemical profiling as an adjunct diagnostic tool.

Keywords: Oral Mucosal Lesions; Inflammatory Infiltrate; Histopathology; Immunohistochemistry; Oral Lichen Planus; Oral Submucous Fibrosis.

Introduction

Chronic oral mucosal lesions constitute a significant proportion of oral pathology cases encountered in clinical practice, presenting diagnostic and therapeutic challenges due to their overlapping clinical and histopathological features [1]. The oral mucosa, serving as the primary barrier against environmental insults, frequently exhibits inflammatory responses that manifest as various pathological conditions ranging from benign reactive lesions to potentially malignant disorders [2].

The inflammatory response in oral mucosal lesions involves a complex interplay of innate and adaptive immune mechanisms, with diverse cellular populations including lymphocytes, macrophages, plasma cells, and mast cells contributing to tissue damage and remodeling [3]. Understanding the specific patterns and compositions of these inflammatory infiltrates is fundamental to comprehending disease pathogenesis and establishing accurate diagnoses [4].

Oral lichen planus represents one of the most common chronic inflammatory conditions affecting the oral mucosa, characterized by T-cell-mediated immunological destruction of basal keratinocytes [5]. The World Health Organization classifies OLP as a potentially malignant disorder, emphasizing the importance of accurate diagnosis

and long-term monitoring [6]. Similarly, oral leukoplakia, defined as a predominantly white lesion that cannot be characterized clinically or pathologically as any other definable lesion, carries varying degrees of malignant transformation risk depending on the presence and severity of epithelial dysplasia [7].

Oral submucous fibrosis, predominantly associated with areca nut chewing habits, represents a chronic progressive condition characterized by juxta-epithelial inflammatory reaction followed by fibroelastic changes in the submucosal tissues [8]. Chronic hyperplastic candidiasis, while primarily infectious in etiology, demonstrates significant inflammatory responses that may contribute to epithelial changes and dysplasia development [9].

Recent investigations have highlighted the significance of specific inflammatory cell populations in disease progression and malignant transformation potential. Studies by Chain et al. demonstrated that increased mast cell density correlates with disease severity in oral submucous fibrosis [10]. Furthermore, research has indicated that the balance between pro-inflammatory and regulatory T-cell populations influences the clinical behavior of oral lichen planus [11].

The immunohistochemical characterization of inflammatory infiltrates has emerged as a valuable diagnostic adjunct, enabling precise identification and quantification of specific cell populations [12]. CD3 and CD20 markers facilitate the differentiation between T and B lymphocyte populations, while CD68 identifies macrophages/histiocytes, and mast cell tryptase specifically labels mast cells [13]. Despite considerable research on individual lesions, comparative studies examining inflammatory patterns across multiple chronic oral mucosal conditions remain limited. This knowledge gap impedes the development of standardized diagnostic criteria and hinders understanding of shared pathogenic mechanisms [14]. Furthermore, the identification of distinctive inflammatory signatures may provide prognostic information and guide therapeutic interventions [15].

Aim: This study aimed to comprehensively compare the histopathological patterns of inflammatory cell infiltrates across four chronic oral mucosal lesions—oral lichen planus, oral leukoplakia, chronic hyperplastic candidiasis, and oral submucous fibrosis—utilizing routine histopathology and immunohistochemical analysis.

Materials and Methods

Study Design and Setting: This cross-sectional analytical study was conducted at the Department of Pathology over a period of 24 months.

Sample Selection

A total of 180 formalin-fixed paraffin-embedded (FFPE) tissue blocks were retrieved from the departmental archives. The sample comprised:

- Oral lichen planus (OLP): n=60
- Oral leukoplakia (OL): n=45
- Chronic hyperplastic candidiasis (CHC): n=35
- Oral submucous fibrosis (OSMF): n=40

Inclusion Criteria:

- Clinically and histopathologically confirmed cases
- Adequate tissue availability for multiple sectioning
- Complete clinical documentation
- Treatment-naïve specimens

Exclusion Criteria:

- Overlapping diagnoses or coexisting lesions
- Previous topical or systemic immunomodulatory therapy
- Specimens with significant processing artifacts
- Immunocompromised patients

Clinical Data Collection: Demographic and clinical information including age, gender, lesion site, duration, and associated habits (tobacco, alcohol, areca nut use) were extracted from patient records.

Histopathological Analysis: Serial sections of 4µm thickness were obtained from each tissue block. Routine hematoxylin and eosin (H&E) staining was performed for morphological assessment. The following parameters were evaluated:

1. **Inflammatory infiltrate intensity:** Graded as mild (<25 cells/HPF), moderate (25-75 cells/HPF), or severe (>75 cells/HPF)
2. **Distribution pattern:** Classified as band-like/lichenoid, perivascular, diffuse, or patchy
3. **Depth of involvement:** Superficial (papillary), intermediate (upper reticular), or deep (lower reticular/submucosal)
4. **Associated epithelial changes:** Atrophy, hyperplasia, dysplasia, or acanthosis

Immunohistochemical Analysis

Immunohistochemistry was performed using the polymer-based detection system. The following primary antibodies were employed:

- CD3 (Clone SP7, 1:100 dilution) for T-lymphocytes
- CD20 (Clone L26, 1:200 dilution) for B-lymphocytes
- CD68 (Clone KP1, 1:100 dilution) for macrophages
- Mast cell tryptase (Clone AA1, 1:50 dilution) for mast cells

Antigen retrieval was performed using citrate buffer (pH 6.0) in a pressure cooker. Appropriate positive and negative controls were included in each batch.

Quantitative Assessment: Cell counting was performed at 400× magnification using a calibrated grid. Five high-power fields (HPF) were randomly selected from areas of maximum inflammatory density, and the mean count was calculated. Two observers performed blinded assessments, and inter-observer reliability was determined using Cohen's kappa coefficient.

Statistical Analysis: Data were analyzed using SPSS version 26.0 (IBM Corporation). Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. One-way ANOVA with Tukey's post-hoc test was employed for multiple group comparisons of normally distributed continuous variables. Kruskal-Wallis test was used for non-parametric data. Chi-square test assessed associations between categorical variables. Statistical significance was set at $p<0.05$.

Results

Demographic Characteristics: The study population comprised 180 patients with a mean age of 47.3 ± 12.8 years (range: 22-76 years). Males constituted 58.9% (n=106) of the sample. The most common lesion site was buccal mucosa (47.2%), followed by tongue (22.8%) and labial mucosa (15.0%).

Inflammatory Infiltrate Intensity and Distribution: Table 1 presents the inflammatory infiltrate characteristics across the four lesion types. OLP demonstrated the highest mean inflammatory cell count (78.4 ± 12.3 cells/HPF), significantly exceeding other lesion types ($p<0.001$). Band-like distribution was predominant in OLP (91.7%), while diffuse patterns characterized OSMF (72.5%) and CHC (60.0%).

Table 1: Inflammatory Infiltrate Characteristics across Chronic Oral Mucosal Lesions

Parameter	OLP (n=60)	OL (n=45)	CHC (n=35)	OSMF (n=40)	p-value
Mean cell count (cells/HPF)	78.4 ± 12.3	52.6 ± 15.7	61.3 ± 14.2	45.8 ± 11.9	<0.001*
Intensity grading, n (%)					
Mild	4 (6.7)	18 (40.0)	8 (22.9)	22 (55.0)	<0.001*
Moderate	21 (35.0)	19 (42.2)	17 (48.6)	14 (35.0)	
Severe	35 (58.3)	8 (17.8)	10 (28.5)	4 (10.0)	
Distribution pattern, n (%)					
Band-like	55 (91.7)	12 (26.7)	6 (17.1)	5 (12.5)	<0.001*
Perivascular	3 (5.0)	14 (31.1)	8 (22.9)	6 (15.0)	
Diffuse	2 (3.3)	11 (24.4)	21 (60.0)	29 (72.5)	
Patchy	0 (0)	8 (17.8)	0 (0)	0 (0)	
Depth of involvement, n (%)					
Superficial	8 (13.3)	24 (53.3)	11 (31.4)	3 (7.5)	<0.001*
Intermediate	45 (75.0)	16 (35.6)	18 (51.4)	12 (30.0)	
Deep	7 (11.7)	5 (11.1)	6 (17.2)	25 (62.5)	

***Statistically significant ($p<0.05$); HPF: High-power field; OLP: Oral lichen planus; OL: Oral leukoplakia; CHC: Chronic hyperplastic candidiasis; OSMF: Oral submucous fibrosis**

Immunohistochemical Profile: Table 2 displays the immunohistochemical quantification of specific inflammatory cell populations. CD3+ T-lymphocytes were significantly elevated in OLP (68.2 ± 8.7%) compared to other lesions ($p<0.001$). CD68+ macrophages were predominant in CHC (42.3 ± 9.1%), while mast cells showed maximum density in OSMF (18.6 ± 4.2 cells/HPF).

Table 2: Immunohistochemical Profile of Inflammatory Cell Populations

Marker	OLP (n=60)	OL (n=45)	CHC (n=35)	OSMF (n=40)	p-value
CD3+ cells (% of infiltrate)	68.2 ± 8.7	45.3 ± 12.4	38.6 ± 10.8	41.2 ± 9.3	<0.001*
CD20+ cells (% of infiltrate)	12.4 ± 4.2	18.7 ± 6.8	14.2 ± 5.1	10.8 ± 3.9	0.024*
CD68+ cells (% of infiltrate)	15.8 ± 5.6	28.4 ± 8.9	42.3 ± 9.1	32.6 ± 7.4	0.003*
Mast cells (cells/HPF)	8.4 ± 2.8	10.2 ± 3.5	9.8 ± 3.1	18.6 ± 4.2	<0.001*
CD4+/CD8+ ratio	1.2 ± 0.4	1.8 ± 0.6	1.5 ± 0.5	2.1 ± 0.7	0.008*

***Statistically significant ($p<0.05$); HPF: High-power field**

Association with Clinical Parameters: Table 3 presents correlations between inflammatory profiles and clinical variables. Significant positive correlations were observed between lesion duration and mast cell density in OSMF ($r=0.62$, $p<0.001$) and between dysplasia grade and CD68+ cell proportion in OL ($r=0.54$, $p=0.002$).

Table 3: Correlation between Inflammatory Parameters and Clinical Variables

Clinical Variable	Inflammatory Parameter	Correlation Coefficient (r)	p-value
OLP			
Disease duration	CD3+ cell density	0.38	0.003*
Clinical severity score	Total inflammatory count	0.52	<0.001*
OL			
Dysplasia grade	CD68+ cell proportion	0.54	0.002*
Lesion size	Total inflammatory count	0.31	0.042*
CHC			
Duration of symptoms	CD68+ cell proportion	0.47	0.005*
Candidal load (PAS score)	Neutrophil count	0.61	<0.001*
OSMF			
Clinical staging	Mast cell density	0.62	<0.001*
Mouth opening	Inflammatory count	-0.55	<0.001*
Areca nut exposure duration	Fibrosis grade	0.68	<0.001*

***Statistically significant (p<0.05); PAS: Periodic acid-Schiff**

Inter-observer agreement for inflammatory cell quantification was excellent (κ=0.87, 95% CI: 0.82-0.92).

Discussion

This comprehensive comparative analysis reveals distinct inflammatory cell infiltrate patterns across chronic oral mucosal lesions, providing valuable insights into disease-specific immunopathological mechanisms. The identification of characteristic inflammatory signatures supports their potential utility as diagnostic adjuncts and prognostic indicators.

Our finding of predominant T-lymphocytic infiltration with band-like distribution in oral lichen planus aligns with established understanding of OLP pathogenesis. The significantly elevated CD3+ T-lymphocyte proportion (68.2 ± 8.7%) corroborates the T-cell-mediated autoimmune etiology of this condition [16]. Previous investigations by Payeras et al. demonstrated similar lymphocytic predominance, attributing basal cell destruction to cytotoxic T-lymphocyte activity directed against modified self-antigens on keratinocytes [17].

The characteristic band-like subepithelial infiltration observed in 91.7% of OLP cases represents a hallmark histopathological feature that distinguishes this condition from other lichenoid reactions [18]. This distribution pattern reflects the tropism of effector T-cells toward the basement membrane zone, where antigen presentation and cytokine-mediated signaling orchestrate the inflammatory response [19].

The elevated macrophage populations in chronic hyperplastic candidiasis (42.3 ± 9.1%) reflect the innate immune response against fungal pathogens. Macrophages serve critical functions in Candida recognition through pattern recognition receptors and subsequent phagocytosis [20]. Our observation of positive correlation between candidal load and neutrophil counts further emphasizes the role of innate immunity in this condition [21].

The significantly increased mast cell density in oral submucous fibrosis (18.6 ± 4.2 cells/HPF) represents a particularly noteworthy finding with substantial pathogenic implications. Mast cells are recognized as potent sources of fibrogenic mediators including transforming growth factor-beta (TGF-β), platelet-derived growth factor, and various cytokines that promote fibroblast activation and collagen deposition [22]. Studies by Kaur et al. previously documented mast cell degranulation in OSMF tissues, correlating with disease progression [23].

The correlation between clinical staging and mast cell density (r=0.62) in OSMF suggests that mast cell quantification may serve as an objective marker for disease severity assessment. This finding has therapeutic implications, as mast cell-targeted interventions could potentially modulate fibrosis progression [24].

Oral leukoplakia demonstrated heterogeneous inflammatory patterns, with the degree of dysplasia significantly correlating with CD68+ macrophage infiltration. Tumor-associated macrophages have been implicated in promoting epithelial transformation through the creation of immunosuppressive microenvironments and secretion of pro-angiogenic factors [25]. The increased macrophage density in dysplastic leukoplakia may represent an early indicator of malignant potential, warranting further investigation in prospective studies [26].

The diffuse inflammatory distribution observed predominantly in OSMF (72.5%) and CHC (60.0%) contrasts sharply with the band-like pattern of OLP, providing a useful discriminating feature. This diffuse pattern in OSMF extends into deeper tissues, consistent with the progressive nature of submucosal fibrosis [27].

The CD4+/CD8+ ratio variations across lesion types offer additional diagnostic utility. The relatively balanced ratio in OLP (1.2 ± 0.4) reflects the involvement of both helper and cytotoxic T-cell subsets, while the elevated ratio in OSMF (2.1 ± 0.7) suggests a helper T-cell predominance potentially driving fibrogenic responses through Th2 cytokine production [28].

Our study limitations include the cross-sectional design, which precludes assessment of temporal changes in inflammatory profiles. Additionally, the study did not evaluate cytokine expression profiles that would provide mechanistic insights into inflammatory responses. Future investigations incorporating longitudinal follow-up and molecular analyses would enhance understanding of disease progression dynamics [29].

The practical implications of these findings extend to diagnostic pathology practice. The implementation of a standardized immunohistochemical panel comprising CD3, CD20, CD68, and mast cell tryptase could enhance diagnostic accuracy in challenging cases with overlapping histomorphological features [30].

Furthermore, the identification of inflammation-associated prognostic markers may guide clinical surveillance protocols and therapeutic decision-making.

Conclusion

This study demonstrates that chronic oral mucosal lesions exhibit distinct inflammatory cell infiltrate patterns that reflect their underlying pathogenic mechanisms. Oral lichen planus is characterized by intense T-lymphocytic infiltration with band-like subepithelial distribution, while chronic hyperplastic candidiasis shows macrophage predominance reflecting innate immune activation.

Oral submucous fibrosis demonstrates significantly elevated mast cell density correlating with disease severity, suggesting a pathogenic role for mast cells in fibrosis progression. Oral leukoplakia exhibits variable patterns with macrophage infiltration correlating with dysplasia grade.

These findings support the implementation of immunohistochemical profiling as a valuable diagnostic adjunct and highlight potential therapeutic targets for inflammatory modulation. The identification of lesion-specific inflammatory signatures enhances diagnostic precision and may guide prognostic assessment and treatment planning in clinical practice.

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