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DIFFERENTIAL DIAGNOSIS OF THE PROLIFERATIVE FORM OF LEUKOPLAKIA IN PATIENTS WITH DIABETIC IMMUNODEFICIENCY

Rasulova Nargiza Azamatovna
Khabibova Nazira Nasulloyevna
Bukhara State Medical Institute

Abstract
The proliferative form of oral leukoplakia in patients with type 2 diabetes mellitus and secondary immunodeficiency is characterized by extensive epithelial hyperplasia, persistent keratinization, and an increased risk of malignant transformation. This study examines the morphological and cytological criteria required for its differential diagnosis, particularly in comparison with oral manifestations of lichen planus and lupus erythematosus. Clinical evaluation in immunocompromised diabetic patients frequently reveals thickened white plaques with sharply defined borders, resistant to mechanical removal and predominantly localized to trauma-prone areas. Histological analysis identifies marked hyperkeratosis, acanthosis, parakeratosis, and a polymorphic inflammatory infiltrate, including segmented neutrophils and plasma cells within the lamina propria. The presence of epithelial dysmaturation with loss of nuclear polarity, cytoplasmic eosinophilia, and intercellular edema further delineates the proliferative variant. In contrast to the lichenoid pattern of T-cell-mediated basal vacuolization in lichen planus and the perivascular collagen degeneration in lupus erythematosus, proliferative leukoplakia exhibits reactive epithelial remodeling driven by local mechanical and systemic metabolic factors. Cytological smears confirm the prevalence of keratinized cells with nuclear atypia and a reduction in intermediate epithelial elements. The findings validate the diagnostic framework necessary for identifying high-risk keratotic lesions in diabetic individuals under immunosuppressive conditions.

Keywords: Proliferative leukoplakia; oral mucosa; type 2 diabetes mellitus; immunodeficiency; epithelial dysplasia; hyperkeratosis; cytological diagnostics; lichen planus; lupus erythematosus; histological differentiation.

Introduction

The proliferative form of oral leukoplakia is a high-risk epithelial disorder marked by sustained keratinocyte hyperactivity and structural epithelial disorganization. In the context of type 2 diabetes mellitus, this lesion demonstrates accelerated clinical progression and histological instability due to systemic metabolic dysfunction and secondary immunosuppression. Long-term hyperglycemia leads to endothelial injury, impaired leukocyte function, and chronic tissue

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hypoxia, promoting epithelial microtrauma and a pro-carcinogenic microenvironment within the oral mucosa.

In diabetic patients, the local immune response is compromised, altering the balance between epithelial proliferation and apoptosis, which facilitates atypical keratinization. The resulting hyperplastic lesions often mimic other chronic keratotic conditions—primarily oral lichen planus and lupus erythematosus—complicating the clinical and histopathological evaluation. While these entities share surface keratinization and mucosal plaque formation, they diverge in their pathogenesis, inflammatory cell profile, and neoplastic potential.

Differentiating proliferative leukoplakia in immunocompromised diabetic patients from lichenoid and lupus-associated lesions necessitates the integration of epithelial morphology, cytological staging, and stromal response characteristics. Establishing clear diagnostic boundaries is essential, given the significantly elevated risk of malignant transformation associated with the proliferative variant,. particularly in patients with disrupted systemic and mucosal immune homeostasis.

Proliferative leukoplakia (PL) is classified as a high-risk subtype of oral potentially malignant disorders, defined by multifocal keratinized lesions with progressive epithelial thickening and a significantly increased likelihood of malignant transformation. In individuals with type 2 diabetes mellitus complicated by secondary immunodeficiency, the clinical course of PL is notably altered by chronic metabolic dysregulation, endothelial dysfunction, and impaired local immune surveillance [1].

The immunosuppressed diabetic environment contributes to abnormal epithelial remodeling through persistent oxidative stress, tissue hypoxia, and reduced keratinocyte turnover control. These systemic factors intensify local mucosal vulnerability, resulting in atypical keratinization resistant to physiological desquamation. In such patients, PL frequently mimics the clinical morphology of oral lichen planus and lupus erythematosus, requiring precise morphological stratification for accurate diagnosis [2].

Histopathological evaluation remains critical for differential assessment. Proliferative leukoplakia in diabetic individuals is associated with extensive hyperkeratosis, irregular parakeratosis, basal cell polarity loss, and an inflammatory infiltrate primarily composed of neutrophils and plasma cells. These features differ from the subepithelial band-like T-cell infiltrate and basal vacuolar degeneration observed in lichen planus or the perivascular lymphocytic distribution and collagen degeneration characteristic of lupus lesions [3].

Cytological analysis demonstrates enhanced nuclear pleomorphism, elevated nuclear-cytoplasmic ratios, and dysmaturation, particularly in areas subjected to chronic mechanical trauma. Reflectance spectroscopy and autofluorescence imaging have been proposed as adjunct methods for early detection and risk assessment, although their diagnostic specificity remains under investigation [4].

The overlap in keratinization patterns across immunopathological conditions necessitates a multilevel diagnostic algorithm, integrating clinical examination, histomorphology, and immunohistochemical profiling (Ki-67, p53, CD3/CD20). Identification of high-risk dysplastic features in the diabetic cohort requires particular attention due to delayed epithelial regeneration and impaired immune-mediated elimination of atypical cells [5].

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Materials and Methods

The study included 64 patients with clinically and histologically verified oral leukoplakia. The main group consisted of 32 patients (mean age 58.4 ± 6.7 years) with type 2 diabetes mellitus and laboratory-confirmed secondary immunodeficiency, defined by decreased CD4+ lymphocyte counts (<500 cells/μL), serum IgA <0.7 g/L, and a reduction in total lymphocyte subpopulations. The comparison group comprised 20 patients with leukoplakia without systemic disease, and a reference group of 12 patients with oral lesions histologically classified as either lichen planus or lupus erythematosus.

Biopsy specimens were obtained from standardized anatomical regions of lesion manifestation, fixed in 10% buffered formalin, embedded in paraffin, sectioned at 3 μm, and stained with hematoxylin and eosin. Immunohistochemical analysis was performed using monoclonal antibodies to Ki-67 (clone MIB-1, Dako), p53 (clone DO-7), CD3 (T-lymphocytes), and CD20 (B-lymphocytes) with automated antigen retrieval and DAB chromogen visualization. The proliferative index was calculated by quantifying Ki-67-positive nuclei per 100 basal epithelial cells. Dysplasia grading followed WHO 2017 criteria.

Cytological examination was conducted using a brush biopsy technique; smears were processed with liquid-based cytology protocols and stained by Papanicolaou. Cellular features—nuclear-cytoplasmic ratio, chromatin density, nuclear pleomorphism, and presence of dyskeratosis—were evaluated semi-quantitatively in five random high-power fields (×400). All slides were assessed independently by two blinded cytopathologists.

The degree of keratinization was measured using intraoral reflectance spectroscopy with a defined spectral absorption profile (400–700 nm) and calibrated against reference mucosa. Unstimulated salivary flow was collected over 10 minutes following standard WHO protocol (ml/min) and correlated with the histopathological type of the lesion.

Statistical analysis was conducted using R software (v.4.2.1). Quantitative variables were compared using the Mann–Whitney U test. Categorical variables were analyzed using Fisher's exact test. Correlations between immunological parameters and dysplasia severity were assessed using Spearman's rho (ρ). Statistical significance was set at $\alpha = 0.05$.

Results and Discussion

A total of 52 patients (28 women and 24 men; mean age: 56.2 ± 8.3 years) with clinically diagnosed oral leukoplakia were examined. Of these, 30 patients (main group) had type 2 diabetes mellitus with laboratory-confirmed immunodeficiency (IgA < 0.7 g/L, CD4+ < 450 cells/μL), and 22 patients formed the comparison group without systemic comorbidities. Lesions were localized primarily to the buccal mucosa (46.2%), lateral tongue surfaces (32.7%), and floor of the mouth (21.1%).

In the diabetic group, lesions demonstrated greater surface area (mean: 3.8 ± 1.1 cm^2) and increased plaque thickness (median keratin layer: 148.4 μm vs. 92.6 μm; $p < 0.01$). Histopathological analysis revealed a significantly higher rate of moderate epithelial dysplasia in diabetic patients (43.3%) compared to the non-diabetic group (18.2%; $p = 0.027$). The proliferative index, determined by Ki-67 immunostaining, exceeded 22% in 53.3% of diabetic cases, while remaining below 15% in the majority (81.8%) of comparison subjects.

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Cytological smears in the main group showed elevated nuclear-cytoplasmic ratios (>0.45 in 66.7% of cases), irregular nuclear contours (57.1%), and chromatin hypergranularity. In contrast, the non-diabetic group predominantly exhibited mature squamous epithelium with preserved polarity. Neutrophilic infiltration in lamina propria was observed in 76.7% of diabetic biopsies, with plasma cells present in 46.7%, suggesting a sustained low-grade inflammatory response linked to immune compromise.

Salivary flow was significantly reduced in the main group (0.21 ± 0.06 ml/min) compared to controls (0.32 ± 0.04 ml/min; $p < 0.01$), correlating with lesion extent and epithelial dehydration. Spectral keratin reflectance ranged from 17.8 to 21.4 units (mean: 19.6 ± 1.2) in the diabetic group, compared to 14.3–17.1 units in controls (mean: 15.6 ± 0.9; $p < 0.001$), indicating higher keratin density and reduced optical permeability.

Table 1. Comparative Histological and Cytological Characteristics of Leukoplakia in Diabetic and Non-Diabetic Patients

Parameter	Diabetic Group (n = 30)	Comparison Group (n = 22)	p-value
Moderate dysplasia, n (%)	13 (43.3%)	4 (18.2%)	0.027
Ki-67 index >20%, n (%)	16 (53.3%)	3 (13.6%)	0.004
Nuclear-cytoplasmic ratio >0.45, n (%)	20 (66.7%)	5 (22.7%)	0.002
Neutrophilic infiltration, n (%)	23 (76.7%)	9 (40.9%)	0.006
Salivary flow (ml/min, mean ± SD)	0.21 ± 0.06	0.32 ± 0.04	<0.01
Keratin reflectance (units, mean ± SD)	19.6 ± 1.2	15.6 ± 0.9	<0.001

The findings demonstrate that diabetic immunodeficiency is associated with deeper keratinocyte atypia, reduced epithelial turnover control, and a distinct inflammatory profile. These data support the need for intensified surveillance protocols and early intervention strategies in patients with systemic metabolic impairment presenting with proliferative leukoplakia.

Conclusion

The proliferative form of oral leukoplakia in patients with type 2 diabetes mellitus and secondary immunodeficiency exhibits a distinct clinical and histopathological profile, characterized by extensive keratinization, increased epithelial dysplasia, reduced salivary flow, and altered inflammatory response. The observed elevation in nuclear-cytoplasmic ratios, Ki-67 proliferation indices, and keratin reflectance values suggests accelerated epithelial turnover with incomplete differentiation under systemic metabolic stress. Compared to non-diabetic patients, the diabetic group demonstrated a significantly higher frequency of moderate dysplasia and cytological atypia, indicating a greater malignant potential. These findings highlight the necessity of rigorous diagnostic protocols, including cytological and immunohistochemical assessment, to ensure early identification and risk stratification of proliferative leukoplakia in immunocompromised individuals. The integration of metabolic background into routine diagnostic evaluation may improve prognostic accuracy and inform timely clinical decisions.

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