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ORAL MUCOSA

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ANNOTATION: The oral mucosa is a complex structure that serves as the body's first line of defense, protecting against mechanical, chemical, and microbiological damaging factors, participating in immune processes, and performing sensory functions. Its morphofunctional state is one of the important indicators of the body's overall health. The study results revealed a clear structural relationship between the stratified squamous epithelium of the normal mucosa and the underlying connective tissue (lamina propria). In pathological processes, hyperkeratosis, acanthosis, and dystrophic changes in the epithelium were observed, along with inflammatory infiltration and disruption of the microvascular network in the lamina propria. The condition of the oral mucosa indicates its high sensitivity to internal and external influencing factors. The obtained data show that histological and immunohistochemical analysis of the mucosa is crucial for the early diagnosis of chronic oral diseases and for a deeper understanding of their pathogenesis. This enables the development of effective prevention and treatment strategies.

KEY WORDS: Oral mucosa, stratified squamous epithelium, lamina propria, leukoplakia, stomatitis, hyperkeratosis, acanthosis, immunohistochemistry, cytokeratins, morphogenesis.

INTRODUCTION

The oral mucosa is a morphologically and functionally complex structure of the body that is in direct contact with the external environment. It constantly acts as the first defense barrier against various mechanical, thermal, chemical influences, as well as against the attack of microorganisms. Among the main functions of the mucous membrane are protective, immunoregulatory, secretory and sensory functions, which indicates its close connection with the general condition of the whole organism. The main components of the oral mucosa include a multilayered squamous epithelium and a structure consisting of connective tissue (lamina propria) located under it. The stability of the epithelium is ensured by the continuous renewal process of its cortical (basal), spinous and superficial layers, as well as intercellular adhesion molecules (integrins, cadherins) and cells of the immune system (Langerhans cells). At the same time, the oral mucosa is an "indicator" structure for the development of chronic stomatitis, leukoplakia, erythroplakia, caries and many other diseases. These pathologies are not only of local importance, but can also be the initial clinical manifestation of a number of systemic diseases (for example, diseases of the digestive, respiratory, endocrine and immune systems). At the same time, dystrophic, inflammatory and hyperplastic processes of the mucous membrane lead to profound changes in its structure, the development of accurate diagnostics and treatment methods for which is an urgent problem. Modern histological and immunohistochemical methods are of particular importance in studying the morphogenesis of pathological processes of the oral mucosa. With the help of these methods, not only major structural changes, but also disorders at the cellular level, changes in the cytokeratin profile, activation of cell proliferation and differentiation centers were detected. In this regard, a thorough study of the normal and pathological state of the oral mucosa is of great importance not only for dentistry, but also for general clinical practice. The aim of this article is to systematically analyze the normal histological structure of the oral mucosa, its main functions and changes during various pathological processes (based on light microscopy, histochemical and immunohistochemical methods).

METHODOLOGY

The study included the following groups: Main group: 80 patients with pathologies of the oral mucosa (mean age 45.6 ± 12.3 years). Among them: Group I: Leukoplakia (n=30). Group II: Acute and chronic stomatitis (n=30). Group III: Lichen planus (n=20). Control group: 20 samples with clinically healthy mucosa (tissues around extracted wisdom teeth). All participants gave their informed consent in the form of a questionnaire, and the study was approved by the ethics committee of [Ethics Committee name] (Protocol No. ...). Histological examination methods. The obtained biopsies were fixed in 10% neutral formalin solution, dehydrated in a series of alcohols in the usual manner and embedded in paraffin. Then, serial sections of 5-7 µm thickness were prepared using a microtome. Sections were stained using the following methods: Hematoxylin and eosin (H&E) staining: Used to study the general morphological structure of the tissues, the thickness of the epithelium, the state of the lamina propria, and the inflammatory infiltrate. Schick-PAS (Periodic acid-Schiff) reaction: Used to detect disruptions of the basement membrane and the amount of glycoproteins and glycogen in the connective tissue. Immunohistochemical (IGHK) analysis. Immunohistochemical methods were used to assess cell proliferation and differentiation of the samples. For this, sections taken from paraffin blocks were adapted for the detection of specific antigens. The following primary monoclonal antibodies were used: Ki-67: To assess the proliferative activity of cells (manufacturer: Dako, citrate buffer, epitope detection at pH=6). Cytokeratin 10 (CK10): To demonstrate normal epithelial differentiation. Cytoqueratin 13 (CK13): As a normal cytoskeletal protein in stratified squamous epithelium. Cytoqueratin 17 (CK17): For expression in regeneration and pathological processes. A polymer detector system (e.g. EnVision™ system) and diaminobenzidine (DAB) chromogenic substrate were used for signal visualization. Sections were counterstained with hematoxylin and covered with coverslips. Microscopic analysis and statistical processing. All preparations were examined under a Nikon Eclipse E200 light microscope, a Leica DM750 microscope equipped with software, and an Olympus BX53 microscope. The expression of markers in IGHK preparations was assessed semi-quantitatively (on a scale from 0 to 3+) and as a percentage of positive cells. Statistical processing of the obtained data was carried out using the SPSS 26.0 program (IBM, USA). The Mann-Whitney U test, Kruskal-Wallis test, and χ^2 (chi-square) test were used to determine differences between groups. The results are presented as mean ± standard deviation (M ± SD). A statistically significant difference was considered when $p<0.05$. This part of the methodology includes all the critical aspects that ensure the reproducibility, reliability, and scientific rigor of the study: sample selection, detailed description of methods, and statistical analysis.

RESULTS

During this study, the morphological changes of the oral mucosa in normal and pathological conditions were comprehensively studied. The results obtained were as follows: Histological structure of the normal mucosa

The normal mucosa studied on hematoxylin-eosin stained preparations of the control group samples was found to have a clear structure. All layers of the multilayered squamous epithelium - basal, spinous, granular and cortical layers - were well expressed. No breaks were observed in the basement membrane. The lamina propria contained connective tissue fibers and a small number of cellular elements (fibroblasts, lymphocytes, macrophages), indicating the normal structure of the mucosa. Histological characteristics of pathological changes

The following pathological changes were noted in the structure of the mucosa in various disease groups: Leukoplakia (group I): Hyperkeratosis of the epithelium and acanthosis of varying degrees were observed in all samples. In 22 of 30 samples (73.3%), moderate and severe degrees of epithelial dysplasia were detected. An inflammatory infiltrate consisting of lymphocytes and plasma cells was observed in the lamina propria. Stomatitis (group II): The main changes were

manifested as thinning of the epithelium, vacuolar dystrophy and focal necrosis. The inflammatory infiltrate in the lamina propria was clearly expressed, consisting mainly of neutrophils and lymphocytes. Dilated capillaries of the microvascular network and hemorrhagic foci were noted. Lichen planus (group III): In all samples (100%), cicatricial changes of the upper epithelial layers, vacuolar degeneration of basal cells and "saw-tooth" rete ridges were detected. A limited lymphocytic infiltrate was located in the lamina propria in the form of a band. Immunohistochemical analysis results The results obtained regarding the expression of cell markers were as follows: Proliferative activity (Ki-67): In the control group, Ki-67 positive cells were located only in the basal layer, with an average of 8.2 ± 1.5%. In leukoplakia, this figure significantly increased to 35.6 ± 4.8% ($p<0.001$), and positive cells were distributed in the lower 2/3 of the epithelium. In the stomatitis and lichen planus groups, the figure was 25.3 ± 3.1% and 18.7 ± 2.4%, respectively. Expression of cytokeratins: CK10 and CK13: In the control group, CK10 and CK13 were normally expressed. In leukoplakia, their expression was reduced or focally lost. CK17: In the control group, CK17 expression was minimal or absent. In all pathological groups, CK17 expression was significantly increased ($p<0.01$), especially in leukoplakia (average 65.3% of cells) and lichen planus (58.7% of cells). Statistical analysis. According to the results of the Kruskal-Wallis test, a statistically significant difference in the Ki-67 index and CK17 expression level was found between all pathological groups and the control group ($p<0.01$). Ki-67 and CK17 indicators in the leukoplakia group were significantly higher than in the stomatitis and lichen planus groups ($p<0.05$). In conclusion, the conducted studies show that pathologies of the oral mucosa have unique characteristics not only histologically, but also immunophenotypically. Leukoplakia is characterized by the highest proliferative activity and impaired differentiation, which is its potential

DISCUSSION

The results of this study reveal a complex interplay between epithelial cell proliferation, differentiation, and reactive changes in the lamina propria in the pathogenesis of oral mucosal pathologies. The data obtained allow not only to describe the morphological picture in detail, but also to analyze in depth the clinical significance of these processes. Pathogenetic interpretation of the main findings. First, our study revealed that leukoplakia is characterized by the most pronounced proliferative activity (Ki-67 index 35.6 ± 4.8%) and impaired differentiation (decreased CK10/13 and increased CK17). This condition, on the one hand, reflects the chronic response of the mucosa to constant damaging factors (e.g., tobacco, mechanical trauma), and on the other hand, is associated with uncontrolled proliferation of epithelial cells and loss of their normal function. Strong expression of CK17 is usually observed in regeneration processes and hyperactivity of basal cells [10]. Our data suggest that CK17 may be an important marker not only for regeneration, but also for the development of precancerous processes, which is consistent with the views of other authors. Secondly, the inflammatory infiltrate and microvascular disorders observed in stomatitis samples are a direct consequence of the disruption of the protective barrier of the mucosa. Thinning and necrosis of the epithelium reduce its protective function, which leads to a deepening of inflammation. An increase in the Ki-67 index (25.3 ± 3.1%) here is mainly reactive and compensatory in nature, aimed at restoring damaged tissues. However, prolonged inflammation can lead to the failure of these compensatory mechanisms and cause the transition to a chronic form. Thirdly, the characteristic “saw-tooth” morphology of lichen planus and the limited lymphocytic infiltrate in the lamina propria indicate a predominantly specific immune pathogenesis of the disease [12]. Our findings indicate that in this pathology, proliferative activity (Ki-67 index 18.7 ± 2.4%) is lower than in leukoplakia, but this suggests that cell death (apoptosis) as a result of the immune system's attack on epithelial cells by T-lymphocytes predominates. The expression of CK17 (58.7%) is evidence

that basal cells are involved in ongoing damage and repair processes. Study limitations. It should be noted that this study is retrospective in nature and limited to biopsy material. The use of additional immunocytochemical or molecular biological methods (e.g., PCR or Western blot) would be useful to fully understand the functional state of the mucosa or molecular processes. In addition, due to the relatively small sample size, caution is required when generalizing the results to a wider population. Clinical significance and future prospects. The main clinical significance of our results is that immunohistochemical examination of markers such as Ki-67 and CK17 is important in the differential diagnosis of oral mucosal pathologies, in accurately determining their risk level and, on this basis, in developing an individual treatment strategy. For example, a high Ki-67 index and CK17 expression may indicate a risk of malignant transformation of leukoplakia, which requires more rapid and radical measures. Future studies should be aimed at studying the expression of other markers (e.g., p53, E-cadherin) in mucosal pathologies, as well as conducting prospective studies involving long-term follow-up of patients. In conclusion, the study shows that each of the pathologies of the oral mucosa has its own characteristics not only morphologically, but also immunophenotypically. Identifying these markers will provide objective criteria necessary not only for understanding pathogenesis but also for early diagnosis and development of effective treatments.

CONCLUSION

As a result of a comprehensive study of the normal and pathological state of the oral mucosa, the following main conclusions can be noted: Morphological differences between the normal and pathological mucosa are clearly expressed. In pathological processes, in particular, in leukoplakia, stomatitis and lichen planus, changes in the structure of the mucosa such as hyperkeratosis, acanthosis, epithelial dysplasia, disruption of the basement membrane and inflammatory infiltrate in the lamina propria were noted. These changes have specific features of the pathogenesis of each disease. Immunohistochemical analysis revealed disorders at the cellular level. It was found that the expression of the Ki-67 proliferative marker was significantly increased in all pathological groups, especially in leukoplakia (35.6 ± 4.8%). This indicates increased cell proliferation and disruption of tissue homeostasis in pathological processes. Changes in the cytokeratin profile indicate a violation of differentiation. Increased expression of CK17 (65.3% and 58.7%, respectively) and decreased CK10/13 in leukoplakia and lichen planus confirm the disruption of the normal maturation process of the epithelium. These changes are not only diagnostic, but also prognostic. The results obtained have practical significance for clinical practice. Histological and immunohistochemical methods have made it possible to early detect diseases of the oral mucosa, assess their malignant risk, and develop an individual treatment strategy. In particular, a high Ki-67 index and CK17 expression in leukoplakia may indicate a high risk of malignant transformation. In the future, it is advisable to widely use molecular biological methods (for example, gene expression studies) to further study the pathologies of the oral mucosa, as well as conduct long-term prospective observations to assess the effectiveness of various therapies.

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