Article

Clinical & Morphological Approach to Diagnosing Periodontium Inflammatory Diseases in Patients with Barrett's esophagus

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Abstract: Barrett's esophagus (BE) is a facultative precancerous ailment affecting the distal esophagus and develops as a complication in 10-15% of patients suffering from gastroesophageal reflux disease (GERD). BE features metaplasia development, where flat differentiated cells are replaced with cylindrical differentiated ones. Inflammatory periodontal pathologies, which – given their high prevalence – are a serious medical and socioeconomic issue faced by society nowadays, account for not tooth loss only, yet also imply a negative impact involving the internal organs, the latter being explained through developing periodontal infection foci. The connection between gastrointestinal tract diseases and the status of the oral organs has behind it metabolic, hemodynamic, immunological, and neuroregulatory issues, as well as disorders of microbiocenosis. Aim of study. This study was aimed at studying the morphological features and the immuno-histochemical profile of Barrett's esophagus in patients with periodontium inflammatory diseases (PID).
Materials and methods. Patients aged 30-65 (n=76), both males and females, with chronic generalized periodontitis (CGP) were divided into the main group (n=37) – patients with BE, and the comparison group (n=36) – showing no general somatic pathology. The control group were patients (n=28) of similar age and gender specifics, featuring neither symptoms of periodontal disease nor signs of esophageal pathology. CGP was diagnosed based on the systematics of periodontal issues as approved at the XVI Plenary Meeting of the All-Union Society of Dentists (1983).The indicators of the diffuse neuroendocrine system and cellular renewal of periodontal, esophageal and gastric epithelial cells were identified employing immunohistochemical studies. The study relied on monoclonal mouse antibodies to NO synthase (ICN, Costa Mesa, USA, titer 1:2000); to endothelin-1 (Sigma, St. Louis, USA, titer 1:200). Polyclonal rabbit antiserum was used against melatonin (CID Research Inc., titer 1:250), whereas the morphometric analysis was performed using the VideoTest-Morphology 5.0 computer image analysis software.
Results. Diseases affecting the esophagus contribute to the progression of periodontal diseases. The analysis of the dental status of patients suffering from PID against BE points at a more significant inflammatory lesion involving the periodontal complex, if compared with patients having no esophageal pathology. The intensity of inflammatory and destructive processes affecting the periodontium in case of BE is due to the functional morphology of endocrine cells of the mucous membrane of the esophagus and gums immunepositive to melatonin, endothelin-1, NO synthase. The obtained data are in line with the respective periodontal indices (Muhlemann, PMA, PI) and may be employed as criteria for early identification of periodontal issue severity. Conclusion. Moderate chronic generalized periodontitis against BE is associated with hyperplasia of esophageal mucosa cells immune-positive to endothelin-1, NO-synthase. Severe chronic generalized periodontitis developing against BE is associated with severe hypoplasia of cells immune-positive to melatonin, as well as with increasing hyperplasia of endocrine cells in the esophageal mucosa producing endothelium-1, NO synthase. The deficiency of melatonin-producing cells along with intense apoptosis causes deeper destructive issues in periodontal tissues. The obtained outcomes of a comprehensive clinical, morphological, immunohistochemical study contribute to expanding the understanding of BE pathomorphology, as well as to clarifying the mechanisms behind PID development in the described category of patients. Reliable diagnostic criteria for the degree of inflammatory and destructive processes affecting periodontium include quantitative analysis of gingival epithelial cells immune-positive to melatonin, endothelin-1, NO-synthase, which allows improving the quality of both treatment and diagnostic measures in patients with PID underway against BE.
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1. Introduction

The medical and social impact of periodontium inflammatory pathology in the entire structure of dental morbidity can be explained by the high prevalence former, namely, 62-94% in the adult population in Russia; the heterogenous nature of etiopathogenetic factors along with the monomorphic type of the respective process; the difficulties associated with detecting periodontium issues at earlier stages; the intensity of the disease course along with a progressive tendency implying further loss of teeth; a decrease in the patient's quality of life [1-6]. The results of research serve a convincing proof to the fact that speaking of the etiopathogenesis of diseases affecting periodontium, a key role is to be assigned to microbial aggression with dental plaque development; colonization resistance of oral tissues, as well as to the status of the hu-moral and cellular elements of the immunity, which are in charge of the periodontium-related structures resistance to negative effects [7-14].

Inflammatory issues in periodontium, which are a set of connective-tissue, microcirculatory and vascular responses to damage, have obvious quantitative differences, yet do not differ significantly in terms of their qualitative manifestations [15-20]. Damaged cellular elements and vessels of the microcirculatory bed, in case of an inflammatory reaction underway, lead to the release of biologically active substances into the surrounding tissues, and all this is decisive for the prevalence, severity and intensity of inflammation, while the most common nosological type is marginal periodontium generalized inflammation [21-26].

Clinical experts have found that the morpho-functional proximity of the periodontal tissues to the gastrointestinal tract (GIT), as well as the unity of the mechanisms behind neuro-endocrine regulation, create grounds for the periodontium pathology comorbidity with digestive organs diseases, namely, with gastroesophageal reflux disease (GERD) [27-29].

Immunohistochemical research methods used to study the epithelium of the periodontium, esophagus and stomach, allows assessing the pathogenetic changes occurring in case of periodontitis against diseases affecting the esophagus and stomach, which will inevitably expand the understanding of the pathogenetic processes under-lying the disease in question. Internal organs pathology of cannot be viewed as an etiological factor; however, it is quite reasonable to consider it as mutually aggravating pathogenetic factors involved in the development of periodontium diseases [30]. The idea of a single diffuse neuroendocrine system was shaped originally in the middle of the 20th Century. The English histochemist E. Pierce proposed the APUD concept, which held that human beings have an additional regulatory system consisting of cells located in the body epithelium and tissues, and which have specific properties related certain cytoplasmic granules filled with bioactive substances. APUD cells are enterochromaffin cells capable of splitting monoamines to produce hormones and bioamines revealing a wide range of biological effects [31]. Gastrointestinal tract tissues are known to secrete over 40 of APUD-system hormones: gastrin, serotonin, melatonin, cholecystokinin, somatostatin, vasointestinal peptide, motilin, enkephalins and endorphins, etc [32]. Recent studies have proven the important role that hormones and diffuse endocrine system (DES) cells play in the development and progression of inflammatory periodontium diseases in patients with gastrointestinal pathologies [33].

Aim of study. The aim of the study was to investigate the indicators of neuro-endocrine cells of the oral mucosa and esophagus, which produce melatonin, endothelin-1 and NO-synthase in patients with periodontitis against Barrett's esophagus.

2. Materials and Methods

This work produced data obtained through the examination of 40 patients with periodontitis against BE; the comparison group included 40 patients with chronic periodontitis with no somatic pathology, whereas the control group included 20 persons with intact periodontitis and who had neither stomach nor esophagus pathology identified in them following a complex examination. The study involved both males and females, aged 30 to 65. Periodontitis, esophageal and gastric diseases were diagnosed subject to clinical recommendations and treatment protocols. The clinical and instrumental examination of periodontitis involved an assessment of the following index indicators: OHI-s (Green J.C., Vermillion J.R., 1964), Muhlemann, modified (Cowell R. et al., 1975), Flesar T. J. (1980), PMA (Parma, 1960), PI (Russel A.L., 1956) and X-ray examination of the dental system. All the patients underwent esophagus-gastro-duodenoscopy (EGDS) performed using an Olympus device with a targeted biopsy of the mucous membrane from the lower third of the esophagus, the antral and the fundus parts of the stomach.

In order to enhance the effectiveness of metaplasia foci visualization when diagnosing BE, chromoendoscopy with methylene blue aqueous solution (0.5%) was performed during endoscopic examination, followed by biopsy of areas revealing in-creased dye absorption; the biopsy material was obtained using the 4-quadrant meth-od. The histological studies were performed with hematoxylin-eosin staining. Barrett's esophagus was considered verified upon detecting intestinal metaplasia in the esophagus biopsies [34]. Immunohistochemical studies were performed using monoclonal mouse antibodies to NO synthase (ICN, Costa Mesa, USA, titer 1:2000); to endothelin-1 (Sigma, St. Louis, USA, titer 1:200); polyclonal rabbit antiserum to melatonin (CID Research Inc. titer 1:250).

Statistical analysis was performed using the standard software package SPSS version 23.0 (IBM SPSS Statistics, USA). The reliability of intragroup differences was assessed using the Wilcoxson matched pairs test, and intergroup differences were assessed using the Mann-Whitney U Test. For indicators with normal distribution, the mean value (M) and its mean error (m) were calculated. When comparing qualitative indicators, Pearson's χ^2-criterion, Fisher's exact test were used. Correlation analysis between variables was performed by Spearman's method. The strength of the correlation relationship between traits was determined taking into account the values of the correlation coefficient r: the correlation relationship was considered "strong" when r was from ± 0.7 to ± 1.0; "moderate" - from ± 0.69 to ± 0.3; "weak" - less than 0.29. Intra- and intergroup differences were considered statistically significant at $p \leq 0.05$.

3. Results and discussion

The average age of the patients with periodontal, esophageal and gastric diseases was 48.7±1.9. All the examined patients with BE had moderate to severe periodontitis, whereas the severity correlated with the GERD duration. 70% of the patients (n=28) with moderate to severe periodontitis had had esophageal diseases for more than 10 years.

An immunohistochemical analysis helped identify the following amounts of epithelial cells in the intact periodontium epithelium: immune-positive to NO-synthase (4.28±0.50; $p \leq 0,05$); to melatonin (9.55±0.43; $p \leq 0,05$); to endothelin-1 (6.02±0.13; $p \leq 0,05$); in the esophagus mucous membrane, the amounts of cells identified were: to NO-synthase – 18.15±0.52; $p \leq 0,05$; to melatonin – 76.57 ± 0.32; $p \leq 0,05$; to endothelin-1 – 30.18 ± 0.40; $p \leq 0,05$. In the antral part of the stomach, the healthy individuals were found to have the following indicators: to NO-synthase – 9.62±0.51; $p \leq 0,05$; to melatonin – 14.61± 0.45; $p \leq 0,05$; to endothelin -1 – 19.24±0.34; $p \leq 0,05$.

Moderate and severe periodontitis featured hypoplasia of cells immune-positive to melatonin (7.20±0.33 and 4.66±0.56, respectively; $p \leq 0,05$), with a significant difference from the similar factor in the comparison group (13.67±2.05 and 12.29±0.32) ($p \leq 0,05$). There has been an inverse correlation detected between the PMA index and the melatonin amount (r=-0.743) in the oral cavity epithelium in patients with severe periodontitis. These changes set grounds for the progression of inflammatory and destructive processes affecting the periodontium, which can be seen through high PMA values (78.67±12.08; $p \leq 0,05$). A decrease in the melatonin immune-positive cells production in periodontal tissues can be seen as a pathogenetic risk factor for the progression of chronic periodontitis. An aggravating factor for periodontitis is Barrett's esophagus, since there was hypoplasia of melatonin-immune-positive cells detected in the esophagus epithelium (from 7.20±0.33 to 4.66±0.56; $p \leq 0,05$) (Fig.1-6).

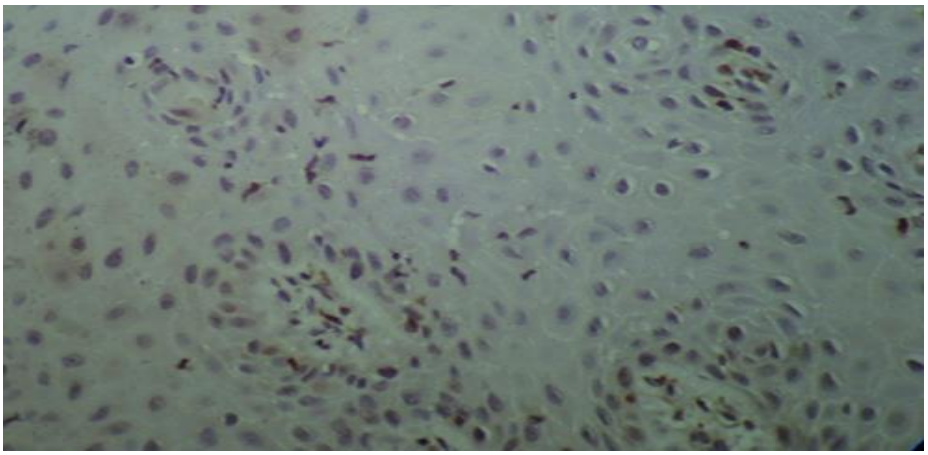

Figure. 1. Patient M., 54 y.o. Diagnosis: chronic generalized periodontitis, severe degree, combined with Barrett's esophagus. Gum biopsy. Few melatonin immune-positive cells. Immunohistochemical method. × 400

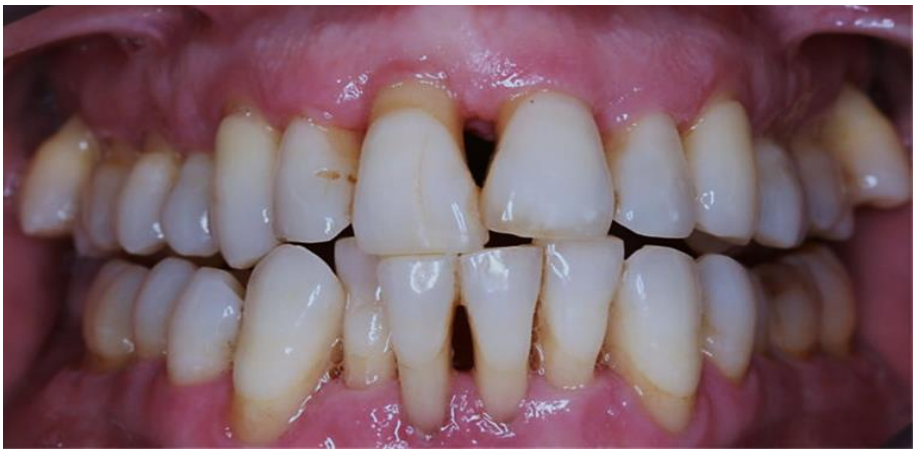

Figure 2. Patient M., 54 y.o. Diagnosis: chronic generalized periodontitis, severe degree, combined with Barrett's esophagus. Clinical picture in the oral cavity

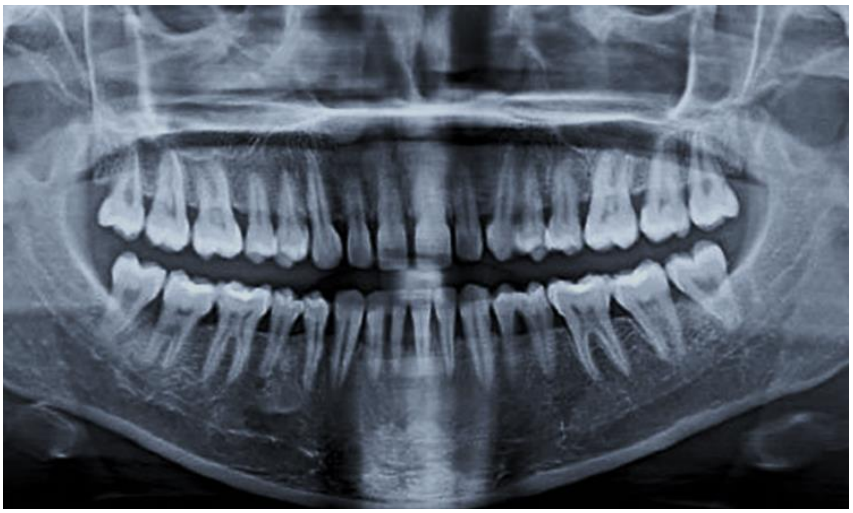

Figure 3. Patient M., 54 years old. Diagnosis: Chronic generalized periodontitis of severe severity combined with Barrett's esophagus. Orthopantomogram

The data we obtained are consistent with that of previous studies aimed at showing differences in the neuroendocrine status depending on the mucosal lesion depth [35-37]. The cases of Barrett's esophagus in their epithelial cells had hyperplasia of esophageal cells producing endothelin-1 (40.09±4.03; $p \leq 0,05$ in case of moder-ate periodontitis and 52.97±2.71; $p \leq 0,05$ – in severe cases) and to NO synthase (54.22±1.35; $p \leq 0,05$ and 58.45±1.71; $p \leq 0,05$, respectively), which exceeded the values in the comparison group (11.14±1.06; $p \leq 0,05$ and 16.62±1.10; $p \leq 0,05$).

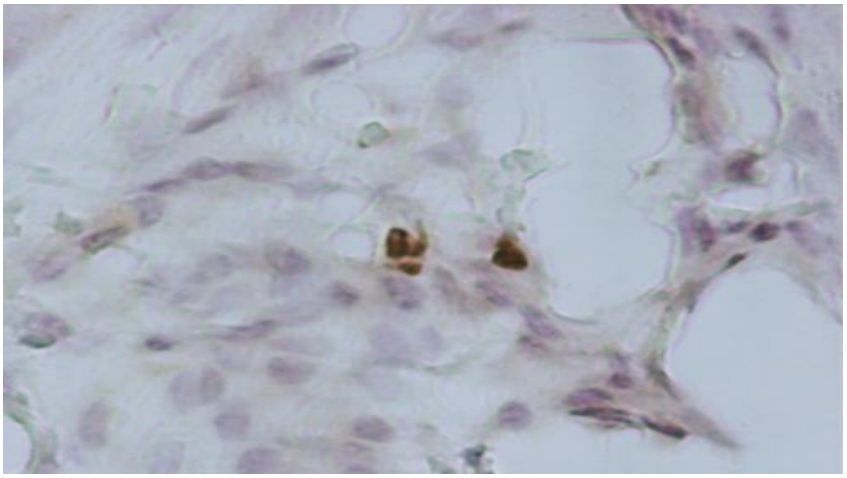

Figure 4. Patient A., 39 y.o. Barrett's esophagus combined with moderate chronic periodontitis. Esophagus biopsy. Few melatonin immune-positive cells. Immunohistochemical method. × 400

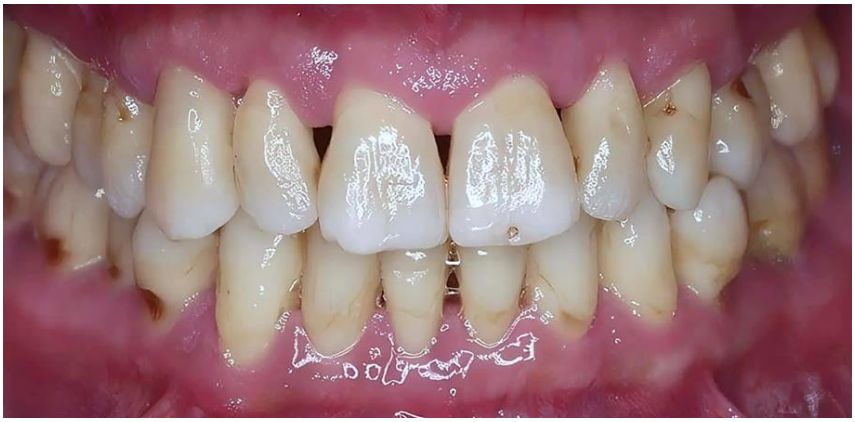

Figure 5. Patient A., 39 years old. Diagnosis: Chronic generalized periodontitis of medium severity combined with Barrett's esophagus. Clinical picture in the oral cavity

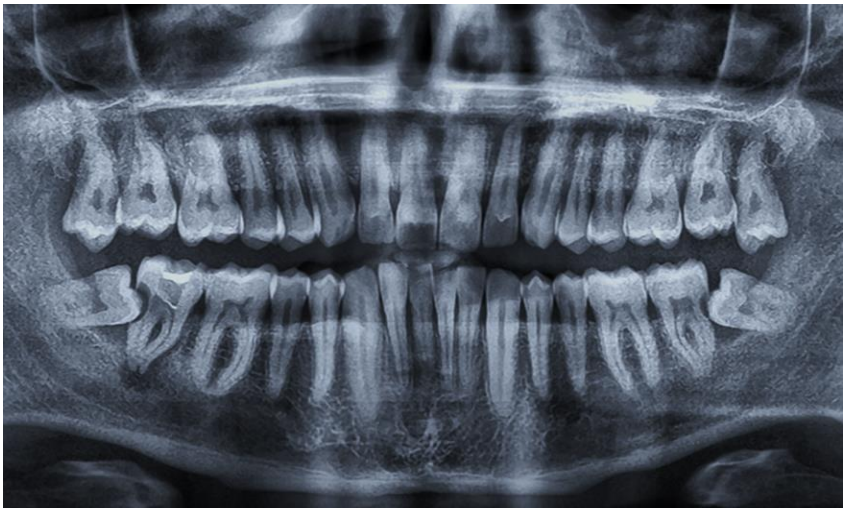

Figure 6. Patient A., 39 years old. Diagnosis: Chronic generalized periodontitis of medium severity combined with Barrett's esophagus. Orthopantomogram

The uniformity of changes in the cells of the diffuse endocrine system of the oral cavity, esophagus and stomach in patients with combined pathology is indicative of a close pathogenetic link involving different anatomical parts of the gastrointestinal tract. The results obtained in the study

offer every reason to suspect melatonin and endothelin-1 involvement in the development of destructive processes affecting the oral cavity, as well as in metaplastic processes in the esophagus mucous membrane. Melatonin can work its effect through the apoptosis induction and by stimulating the activity of endothelin-1producing epithelial cells.

Gastroesophageal reflux disease (GERD) and Barrett's esophagus develop against significant atrophic and inflammatory changes going on in the stomach. Changes in the stomach antrum initiate and maintain desynchronized functioning of the lower esophageal sphincter, the leading cause of GERD. A feature typical of GERD is disturbed quantitative specifics and functional activity of cells producing endothelin-1 and NO synthase.

4. Conclusion

Studying periodontitis against BE led us to make a conclusion concerning the aggravating effect that the digestive tract pathology will have on the course of periodontitis. Moderate and severe chronic periodontitis against BE developed on the backcloth of hyperplasia of cells producing endothelin-1 and NO-synthase, whose physiological effects trigger an intense inflammatory process in the periodontium.

Hypoplasia of melatonin-immune-positive cells leads to disrupted regeneration in the periodontal tissues and progressing destructive inflammation. The main parameters detected in the mucous membrane of the periodontium, esophagus and stomach mean that the identified changes belonged to the same type. The analysis of the obtained outcomes shows that the regulation of the processes involving the digestive tract cells population is synchronic, while the pathological changes occurring in different parts of the digestive system have a mutually negative effect on one another.

Application of artificial intelligence:

The article is written without the use of artificial intelligence technologies.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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