Effect of drug-induced pathomorphosis on oral cavity organs and tissues in chronic obstructive pulmonary disease combined with coronary heart disease: A clinical case

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ABSTRACT
This article describes a clinical case of a patient, as well as literature data confirming the direct mutual influence of lesions in the oral cavity and the bronchocardiac complex pathology. Special attention is paid to the side effects of the main drugs prescribed in the basic therapy of chronic obstructive pulmonary disease, combined with coronary heart disease. It is noted that the drug-induced pathomorphosis can cause the development of periodontal lesions. Insufficient knowledge of these issues and the practical need for corrective measures to be taken by dentists with this category of patients warrant the relevance of research in this direction.

Key words: chronic obstructive pulmonary disease, coronary heart disease, periodontal, gum epithelium

INTRODUCTION
Diagnostics and treatment of pathological changes in the oral cavity related to somatic diseases are an important aspect of successful work of dentists around the world. Most diseases of the internal organs provoke changes in the oral cavity, exerting both direct and indirect effects on the pathways involved in the lesion's pathogenesis. It was found that periodontal disease can accompany somatic pathology in 20 — 25% of cases. Type 2 diabetic individuals with severe periodontal disease were identified to have 3.2 times the risk of mortality due to ischemic heart disease compared to individuals with no or mild periodontal disease.1,2

One of the most common somatic diseases that causes various dental lesions is chronic obstructive pulmonary disease (COPD), which is associated with high prevalence and anatomical-functional unity with the oral cavity organs. According to the data of Shen TC et al., it has been shown that patients with COPD are at a higher risk of developing periodontal diseases than the general population. In addition, patients who receive corticosteroid treatment are at a higher risk of developing periodontal diseases.3,4 Large-scale epidemiological studies have shown a close interconnection of COPD and coronary heart disease (CHD), which is associated with common links in pathogenesis.5

In patients who suffer from COPD combined with CHD, in addition to systemic inflammation, there are changes in linear and volumetric blood flows, as well as the violation of regional hemodynamics of the periodontium.6 According to the data of Usher AK and Stockley RA, patients with severe chronic periodontitis have an increased risk of developing cardiovascular disease, in part, due to the effect of the systemic cytokines and also bacterial products on vascular endothelial cells, resulting in the development and progression of vascular plaques.7 Moreover, with unsatisfactory oral hygiene, microorganisms and their genes enter the bloodstream and can be found in atherosclerotic plaques, causing cross-immune reactions8,9.

Bronchodilators (β2-agonists of short and long action), anticholinergic drugs, and inhaled corticosteroids (ICS) are used as the main drugs for COPD.10 However, with frequent inhalation administration using metered-dose aerosol inhalers or in cases of violating the technique of their use, as a rule, only about 10 — 20% of the drug reaches the target, while 80 — 90% is deposited in the oral cavity, causing various dysfunctions of the immune defense systems.11

Herein is a case history of a 38-year-old patient who was referred for an in-depth dental examination by a cardiopulmonologist due to complaints. The clinical diagnosis included the following: chronic obstructive pulmonary disease, chronic cor pulmonary, stage 2 pulmonary hypertension, hypertension stage II, 3 degrees, and heart failure stage II A with preserved left ventricular ejection fraction.
Fluticasone, salmeterol, berodual, amlodipine, cardiomagnil, lisinopril, and atorvastatin had been taken as basic therapy by the patient for a long time. During the dental examination, the patient complained of constant dry mouth, distorted taste sensations, burning tongue, painful teeth sensitivity, and bleeding of gums when eating. The patient associated all complaints with the long-term intake of a large number of medications.

MATERIAL AND METHODS

This study was conducted in accordance with the amended Declaration of Helsinki. The Institutional Review Board of Government Institution “L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine” approved the study, and the participant provided written informed consent. A dental examination was carried out with the registration of complaints and data from the patient’s life and illness history. The unstimulated oral fluid was collected in the morning on an empty stomach in graduated tubes for 10 – 20 minutes. To assure data homogeneity, the patient was warned about the prohibition to perform hygienic procedures in the oral cavity, to chew gum, and/or to smoke before the manipulation. The rate of salivation (reference values: 0.3 – 0.6 ml/min), the oral fluid viscosity (norm value: in the range of 1.8 – 4.1 relative units), and pH value of mixed saliva (norm value: in the range of 6.8 – 7.2) were calculated. Immunological reactivity of oral tissues was studied by the level of secretory Immunoglobulin A (sIgA) in mixed saliva using the enzyme immunocassay with a set of reagents («Секреторный IgA-ИФА» «ХЕМА», Russia). Cytological and immunocytochemical studies were carried out on scrapings from the gum epithelium. To assess the cellular composition (neutrophils, monocytes, and lymphocytes), the preparations were stained with hematoxylin-eosin (H&E), photographed, and selected for analysis in sets of 20 images of cells with clear boundaries. To obtain photographs of cells, a digital video camera CAM 2800 (lens x40, eyepiece x10) was used. For histological examination, a biopsy material obtained from the area of the gingival papilla was used. Sections (5-μm thick) were stained with H&E.

RESULTS

Upon admission, the general condition of the patient was of moderate severity. Consciousness was clear, and the position was active. The skin and visible mucous membranes were clean. There was expansion of the cervical veins. Peripheral lymph nodes were not enlarged, and there was an increase in the anteroposterior chest size (barrel chest). In the lungs, percussion pulmonary sound was auscultatory with weakened wheezing (dry scattered wheezing; NPV 20 beats per minute). The borders of relative cardiac dullness were: right (in IV m/s, according to L. parasternalis dextra), upper (in III m/r, according to L. parasternalis sinistra), and left (according to L. clavicularis media in V m/r). There were muffled heart sounds and splitting of the 2nd heart sound with an emphasis on the pulmonary artery. Additionally, the murmur of the tricuspid valve was insufficient and rhythmic. Blood pressure was measured on the left arm after 5 minutes of rest in a sitting position (110/90 mmHg). Pulse was 94 beats per minute and rhythmic. The abdomen was soft and painless on palpation. Moreover, the liver did not protrude from the edge of the costal arch, Pasternatsky symptom was absent/negative on both sides, and the feet and legs were pasty. During the dental examination, the red border of the lips was found to have no pathology. The mucous membrane of the cheeks and lips had dental prints, along with the teeth closing line, and was edematous. On the cheek, along with the teeth closing line, the mucous membrane was of whitish opacity and tightly adhered to the surface. Palpation of the mucous membrane at the site of the lesion was painless (Figure 1).

The tongue was moderately moist, edematous, and covered with a whitish plaque on the back, which could be easily removed from the surface. At the time of examination, the gum was swollen and congestive hyperemic, while the gingival papillae did not adhere tightly to the teeth surface (Figure 2). Bad breath was detected. Further probing was conducted: bleeding (2.1 per Papillary Bleeding Index (PBI), papillary-marginally-alveolar index (PMA) - 25.0%, Complex periodontal index (CPI) - 3.0, periodontal pockets were 4.8 mm deep, dental deposits were revealed in large quantities in the form of supragingival and subgingival deposits, and the Green-Vermilion hygiene index was 2.6 (poor oral hygiene).

In the areas 14, 13, 12, 11, 21, 22, 23, 31, 32, 33, 34, 35, 41, 42, 43, 44, 45, there was limited 2nd degree recession of the gingiva. X-ray examination results showed the following: destruction of the cortical plate, and foci of alveolar bone destruction with violation of the alveolar ridge 1/3 – 1/2 of the teeth root length. The diagnosis was chronic generalized periodontitis of moderate severity. Saliva was white, frothy, and viscous, and in insufficient quantity. The salivation rate was 0.26 ml/min.
Figure 1: Picture of the oral cavity of the patient with the diagnosis: chronic obstructive pulmonary disease, chronic cor pulmonale, stage 2 pulmonary hypertension, hypertension stage II, 3 degrees. Heart failure stage II A with preserved left ventricular ejection fraction. Whitish opacity of the cheek mucous membrane in the teeth closing line projection is observed.

Figure 2: Picture of the gingival margin in the frontal part of the oral cavity of the patient with the diagnosis: chronic obstructive pulmonary disease, chronic cor pulmonale, stage 2 pulmonary hypertension, hypertension stage II, 3 degrees. Heart failure stage II A with preserved left ventricular ejection fraction.
viscosity was 3.6 relative units, and pH was 6.4. The secretory IgA level reached 71.663. During the histological examination of gums, attention was drawn to the almost widespread thickening of stratified squamous epithelium and the phenomenon of parakeratosis. Stratification of layers was violated; the epithelial cells met the phenomena of protein parenchymal dystrophy, and the presence of the dysplasia phenomenon was manifested by a violation of layer stratification, increase in the nuclear-cytoplasmic index, hyperchromic nuclei, and the presence of single mitoses (Figure 3). A detailed cytomorphometric study of scrapings from the gingival epithelium revealed that the number of parabasal cells was 1%, intermediate — 24%, superficial — 33%, and keratinizing — 42% (Figure 4). Immunocompetent cells were distributed as follows: leukocytes — 22%, neutrophils — 89%, monocytes — 5%, and lymphocytes — 6%.

**DISCUSSION**

The patient's main dental complaint was persistent, intense dryness in the mouth. Besides, the patient complained of taste sensations, distortion, burning tongue, painful sensitivity of teeth, and bleeding of gums when eating. It is known that saliva performs many functions, the main of which are protective (moisturizing the oral cavity tissues, utilizing food debris and epithelium, and forming the barrier against antibodies and other active substances), and trophic (maintaining constant hydration and physiological regeneration of the mucous membrane). However, the oral fluid performance of its functions depends on its biophysical properties.

Sialometry showed that the reduced salivation rate changed the oral fluid’s rheological properties, increased its viscosity, and impaired its cleansing ability. It can be presumed that a significant factor in the development of xerostomia is drug pathomorphosis caused by drug polypharmacy, consisting of simultaneous use of a large number of drugs with xerogenic properties. For example, β-2-agonists act on inhibition of saliva secretion by affecting β-2 receptors of glands saliva; asthmatic patients treated with β-2-adrenoceptor agonists have an increased caries susceptibility due to an impaired saliva secretion caused by the use of beta-adrenergic agonists.

On the other hand, β-blockers and ACE inhibitors contribute to the reduction in renin–angiotensin–aldosterone system (RAAS) activity. They assure the decrease of pressure in blood vessels, vasodilation, and decrease in the volume of regional blood flow, including in the parenchyma of the salivary glands, which can lead to the indicated effects. It was found that patients under beta-blocker therapy presented reduced non-stimulated salivary flow when compared to controls, without influencing the sense of taste or masticatory performance. Our study observed an increase in slgA levels, which is not consistent with the data of Fukushima C et al. (2005), which states that inhaled corticosteroids can potentially decrease total salivary IgA. However, an increase in this indicator may be the consequence of unsatisfactory oral hygiene and significant antigenic irritation of tissues by microorganisms, indicating activation of the humoral link of pathogenesis; thus, aims at eliminating foreign agents can normalize impaired homeostasis. Also, the reason for the increased slgA level may be poor oral hygiene and significant antigenic irritation of tissues by microorganisms. Besides, we considered increasing the level of slgA as the compensatory response of saliva for restoration of deficiency of immunoglobulins belonging to other classes. Moreover, we considered the factors of nonspecific defense (lysozymes), as well as direct manifestations of nonspecific inflammation, that accompany COPD. The patient showed an increase in the number of surfaces and keratinizing cells of the epithelium, that is, those at the final stages of their differentiation.

The particular feature of a healthy oral mucosa is the constant regeneration of epithelium. Epithelial cells are at different stages of their morphofunctional development and gradually move from poorly differentiated to highly specialized cells. As they mature, they shift to the surface layers, undergoing desquamation. This fact is confirmed by the work of Benazir MI et al. (2020), which showed that prolonged use of inhalational drugs in patients diagnosed with asthma is associated with changes in oral epithelial cells. However, in the periodontium pathological conditions, a violation occurs in the stages of differentiation, leading to pathological exfoliation. An increase in the desquamation process is observed and changes the relationship between different types of epithelial cells. Thus, the functional status of cells depends on the degree of their maturity.

**CONCLUSION**

Therefore, upon summarizing the findings of this clinical case, we postulate that the development and progression of changes in the oral cavity may be associated with both COPD and CHD, especially against the background of long-term medication intake. The
nature of the relationship of such lesions is multifaceted; that is, on the one hand, occurrence, intensity, and course of changes in the oral cavity depend on the severity of the somatic pathology; and the other hand, the pathology in the oral cavity negatively affects severity and course of diseases of the internal organs.

Understanding and studying the possible relationship between lesions in the oral cavity and systemic pathology, especially with prolonged or constant use of basic therapy drugs, is of high importance, both on the part of a patient and a dentist internist.

CONSENT

Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.
ABBREVIATIONS

COPD: chronic obstructive pulmonary disease  
CHD: coronary heart disease  
PqH: pH value

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AUTHOR’S CONTRIBUTIONS

N.E. conceived of the study, carried out the clinical studies, drafted the manuscript, Data analysis Guarantor; I.K. Literature search, Clinical studies, participated in the design of the study, Data acquisition, Data analysis. All authors read and approved the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS

The basic clinical data used to support the findings of this study are included within the article. The data used to support the findings of this study are restricted in order to protect patient’s privacy, but available from the corresponding author upon request. (To contact Dr. N. Emelyanova nattadenta@gmail.com)

CONSENT FOR PUBLICATION

The authors hereby consent that the publisher publishes the work.

CONFLICT OF INTEREST

There is no conflict of interest.

REFERENCES

1. Cassol-Spanemberg J, Rodríguez-de Rivera-Campillo ME, Otero-Rey EM, Estrugo-Devesa A, Jané-Salas E, López-López J. Oral lichen planus and its relationship with systemic diseases. A review of evidence. J Clin Exp Dent. 2018;10(9):e938–e946. PMID: 30386529. Available from: https://doi.org/10.4317/jced.55145.

2. Preshaw PM, Bissett SM. Periodontitis and diabetes. Br Dent J. 2019;227(7):577–584. PMID: 31605062. Available from: https://doi.org/10.1038/s41415-019-0794-5.

3. Baldomero AK, Siddiqui M, Lo CY, Petersen A, Pragman AA, Connett JE, Kunisaki KM, Wendt CH. The relationship between oral health and COPD exacerbations. International journal of chronic obstructive pulmonary disease. 2019;14:881–892. PMID: 31114185. Available from: https://doi.org/10.2147/COPD.S194991.

4. Shen TC, Chang PY, Lin CL, et al. Risk of periodontal diseases in patients with chronic obstructive pulmonary disease: a nationwide population-based cohort study. Medicine (Baltimore). 2015;94(46):e2047. PMID: 26020394. Available from: https://doi.org/10.1097/MD.0000000000000874.

5. Carter P, Lagan J, Fortune C, Bhatt DL, Vestbo J, Niven R, et al. Association of Cardiovascular Disease with Respiratory Disease. J. Am Coll Cardiol. 2019;73(17):2166–2177. Available from: https://doi.org/10.1016/j.jacc.2018.11.063.

6. Carrizales-Sepúlveda EF, Ordaz-Farias A, Vera-Fineda R, Flores-Ramírez R. Periodontal Disease, Systemic Inflammation and the Risk of Cardiovascular Disease. Heart Lung Circ. 2018;27:1327–1334. Available from: https://doi.org/10.1016/j.hlc.2018.05.102.

7. Usher AK, Stockley RA. The link between chronic periodonti-tis and COPD: a common role for the neutrophil? BMC Med. 2013;11:241. PMID: 24223906. Available from: https://doi.org/10.1186/1741-7015-11-241.

8. Cairo F, Gaeta C, Dorigo W, Oggioni MR, Pratesi C, Pini Prato GP, Pozzi G. Periodontal pathogenes in atheromatous plaques. A controlled clinical and laboratory trial. J Periodontal Res. 2004;39(6):442–446. PMID: 15491349. Available from: https://doi.org/10.1111/j.1600-0765.2004.00761.x.

9. Atarbashi-Moghadam F, Hasei S, Hasei SA, Hosseini NS, Behdadmehr G, Atarbashi-Moghadam S. Periodopathogens in atherosclerotic plaques of patients with both cardiovascular disease and chronic periodontitis. ARYA Atheroscler. 2018;14(2):53–57. Available from: 10.22122/arya.v14i2.1504.

10. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2019. Available from: www.goldcopd.com.

11. Chen S, Small M, Lindner L, Xu X. Symptomatic burden of COPD for patients receiving dual or triple therapy. Int J Chron Obstruct Pulmon Dis. 2018;13:1365–1376. Available from: doi.org/10.2147/COPD.S163717.

12. Liena-Puy C. The rôle of saliva in maintaining oral health and as an aid to diagnosis. Med Oral Patol Oral Cir Bucal. 2006;11(5):E449–E455. PMID: 16878065.

13. Ryberg M, Möller C, Ericson T. Saliva composition and caries development in asthmatic patients treated with beta 2-adrenoceptor agonists: a 4-year follow-up study. Scand J Dent Res. 1991;99(3):212–218. PMID: 1871531. Available from: https://doi.org/10.1111/j.1600-0722.1991.tb1887.x.

14. Matos LF, Pereira SM, Kaminagakura E, Marques LS, Pereira CV, van der Bilt A, Pereira LJ. Relationships of beta-blockers and anxiolytics intake and salivary secretion, masticatory performance and taste perception. Arch Oral Biol. 2010;55(2):164–169. PMID: 20018274. Available from: https://doi.org/10.1016/j.archoralbio.2009.11.011.

15. Fukushima C, Matsuse H, Saeki S, Kawano T, Machida I, Kondo Y, Kohno S. Salivary IgA and oral candidiasis in asthmatic patients treated with inhaled corticosteroid.J.Asthma. 2005;42(7):601–604. PMID: 16169797. Available from: https://doi.org/10.1080/02770900500216259.

16. Bozejac BV, Stojin I, Duric M, Zvedzin B, Brkanic T, Budišin E, Vukoić K, Šecen N. Impact of inhalation therapy on the incidence of carious lesions in patients with asthma and COPD. J Appl Oral Sci. 2017;25(5):506–514. PMID: 29069148. Available from: https://doi.org/10.5041/RMMJ.10405.

17. Takeuchi K, Matsumoto K, Furuta M, Fukuyma S, Takeshita T, Ogata H, Suma S, Shibata Y, Shimazaki Y, Hata J, Ninomiya T, Nakanishi Y, Inoue H, Yamashita Y, Ninomiya T, Nakanishi Y, Inoue H, Yamashita Y. Periodontitis Is Associated with Chronic Obstructive Pulmonary Disease. J Appl Respir Physiol. 2019;98(5):534–540. PMID: 30848974. Available from: https://doi.org/10.11171/0020234519833630.

18. Benazir MI, Prasad H, Rajmohan M, Srichinthu KK, Prema P, Mahalakshmi L, Kumar GS. Effect of Inhalational Therapy on Bucal Musosal Cells in Asthmatic Patients: A Cytological Study. Rambam Maimonides Med J. 2020;11(4):e0031. PMID: 32441649. Available from: https://doi.org/10.5041/RMMJ.10405.