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Regarding the question of the course of combined cardiorespiratory pathology as to the condition of cellular immunity in patients with acute exacerbation of COPD of the IIIrd degree of severity, groups C and D

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Abstract
The purpose of this research – is to study T- and B-cell immunity in chronic obstructive pulmonary disease (COPD) of the IIIrd degree of severity, groups C and D. The study involved 72 patients. All patients with acute exacerbation of COPD III degree of severity were randomized into two groups. The first group included 28 patients with isolated course of COPD IIIrd degree of severity, groups C and D; the second group consisted of 44 patients with acute exacerbation of COPD IIIrd degree of severity combined with stable ischemic heart disease (SIHD), stable angina pectoris (SAP). Depending on the version of the SIHD course, patients of the second group were divided into two subgroups. The main subgroup included 26 patients with concomitant SIHD SAP I-II FC. The subgroup of comparison included 18 patients with comorbid SIHD SAP I-II FC. According to the result of examination, irregularities were detected, which characterize the cellular components of the immune response.

Keywords: COPD concomitant SIHD, comorbid SIHD, SAP, cellular immunity, lymphocytes

Introduction
At the heart of COPD there is chronic inflammation in the broncho-pulmonary system, which violates the integrity of the epithelial layer and triggers broncho- constrictor reaction [1]. Chronic airway inflammation in COPD is caused by a complex of immune-pathological and morphological changes [2]. Today, the presence of chronic inflammation in bronchopulmonary system by many authors is considered as clinical manifestation of secondary immunodeficiency [2-5]. Violations of cellular and humoral immunity are equally important in increasing the frequency of exacerbations of COPD and disease progression. It is proved that the irregularities in the immune state are one of the main factors that determine the nature of COPD exacerbation and characteristics of its clinical course [6-9]. We know that COPD can run both independently and in conjunction with concomitant diseases or systemic effects [10-13]. The most studied are metabolic and muscular-skeletal system effects (skeletal muscle dysfunction, weight loss, osteoporosis, anemia, and polycythemia and others), that could significantly impair its course; that defines comorbidity [12, 14]. One of the potential systemic effects of COPD is considered cardiovascular pathologies, among which the most important are the damage of endothelium with the development of endothelial dysfunction of and extra-coronary vessels, metabolic cardiomyopathy, coronary artery disease, arterial hypertension and pulmonary hypertension with subsequent development of chronic pulmonary heart disease [15-18]. It is suggested that the actual persistent inflammation characteristic of COPD, and the associated immunological disorders, invest major contribution to the pathogenesis of cardiovascular diseases, including coronary heart disease [19, 20].

Objective of the study: To study T- and B-cell immunity during exacerbation of COPD of the IIIrd degree of severity, groups C and D in patients with isolated course and combined with SIHD SAP I-II FC before the treatment.

Materials and methods: The study involved 72 patients –60 men (83.33%) and 12 (16.66%) women. All patients with acute exacerbation of COPD of the IIIrd degree were randomized into two groups. The first group included 28 patients with isolated course of COPD of the IIIrd degree; the second group consisted of 44 patients with acute exacerbation of COPD of the IIIrd degree combined with SIHD SAP I-II FC. The average age of patients in groups I and II respectively

was (58.3±6.2) and (59.3±8.1) years. Depending on the version of SIHD course, patients of the second group were divided into two subgroups. The main subgroup included 26 patients with concomitant SIHD I-II FC; a subgroup of comparison included 18 patients with comorbid SIHD I-II FC. Regulatory indicators of T-cell immunity were studied in 16 PHP (practically healthy persons).

The diagnosis of comorbid SIHD is confirmed in the dynamic clinical, laboratory and instrumental studies in the hospital during treatment of the latest exacerbation by the criteria that have been developed in our clinic. Diagnosis of concomitant coronary artery disease was based on the evidence of myocardial infarction (extract from outpatient's card, characteristic changes on ECG) as well as the typical clinical manifestations of angina, which were confirmed by instrumental methods.

Determining the population and the subpopulation contents of peripheral blood lymphocytes was carried out by identifying differentiated antigens in immunofluorescence test with monoclonal antibodies belonging to clusters of differentiation. Preparations were examined in fluorescent microscope equipped with phase-contrast adjustment "Lyumam-IZ". Statistical analysis of the results and calculations were performed using SPSS 10.0 for Windows.

Results of the study and their discussion. Many studies have shown that precursors of lymphoid cells are differentiated in T- or B-cells depending on the microenvironment in which they are located. The many effects, which T-cells have as part of the immune response, are associated with the implementation of various functions of their subpopulations. It is known that T-cells in their composition have two regulatory substances: T-helper-effectors (CD4+) and T-killer-suppressors (CD8+), which determine the direction of the immune response to various antigenic substances. T-cells have on their surface T-cell antigenic receptor and CD3+ marker that is a complex of five polypeptides involved in the transmembrane signal transmission in the activation of T-lymphocyte. In contrast, B-cells have on their surface superficial immunoglobulin, which is the antigen receptor and determining marker [21, 22].

During comparative study of lymphocyte population indicators (Table 1) major changes in patients with combined CRP (cardiorespiratory pathology), particular in subgroup of comparison were identified. Thus, the level of CD3+ lymphocytes in this category of patients was (49.09±3.08%), that is 1.27 times (p<0.01) lower than in the PHP, and 1.21 times (p<0.05) lower compared with patients with isolated course of COPD. Index of CD3+ of T-cells in patients of main subgroup was lower 1.04 times (p> 0.05) compared with patients of the first group and 1.15 times higher (p<0.05) compared with group of comparison.

Index of CD4+ of T-cells in patients with acute exacerbation of COPD of the IIIrd degree without comorbidity before the treatment was significantly reduced by 14.82% (p<0.05) compared with group of PHP, which was (43.26±2.74%). However, the level of CD4+ lymphocytes in patients with combined CRP, including COPD in combination with comorbid CIHD, was (29.10±2.97%), that 1.48 times significantly lower compared with a group of PHP. Such changes of CD4+ of T-cells, we have noted in patients of the main subgroup (COPD + concomitant coronary artery disease). Therefore, for patients with acute exacerbation of COPD IIIrd degree both in isolated course, and in combined CRP, immunodeficiency is typical, which manifests itself as a reduction of the total contents of lymphocytes (CD3+) and T-helper cells (CD4+ lymphocytes).

Table 1: Indicators of cellular link of immunity in patients with acute exacerbation of COPD of the IIIrd degree of severity

Indicators / groups of examined	Control group (n=18)	First group (n=28)	Main subgroup (n=26)	Subgroup of comparison (n=18)
CD3+ lymphocytes, %	62.4±3.72	59.3±2.78	56.8±2.98	49.09±2.08#
CD4+ lymphocytes, %	43.26±2.74	41.96±2.71	37.14±2.41	29.10±2.97#
CD8+ lymphocytes, %	23.9±3.16	26.2±2.08	26.9±2.38	28.36±3.22
CD16+ lymphocytes, %	16.98±0.13	15.06±0.35^	13.6±0.46*	13.51±0.71
CD22+ lymphocytes, %	22.4±0.35	24.9±1.48^	20.2±0.67*	19.96±0.43

Note. * - p<0.05 – between indicators of control and main subgroups; ^ - p<0.05 – between indicators of the first group and principal subgroup; # - p<0.05 – between indicators of the control group and subgroup of comparison.

It is known that T-killers/suppressors (CD8+ -lymphocytes) – are brake regulatory cells. They make up about 20-30% of circulating lymphocytes. Specific T-suppressors inhibit the immune response to the antigen defined, and non-specific T-suppressors inhibit the immune response regardless of the antigen by regulating cellular proliferation. The development of autoimmune, immunodeficiency, blastomatous processes and reactions of transplantation immunity depends on the functional state of T-suppressors and their contents in peripheral blood [22].

Increase of the relative number of CD8+ lymphocytes can occur in the presence of infection at the time when there is an increase in the specific cytotoxic cells. Similar changes are observed in oncologic diseases in allotransplantation. Reduction of the relative number of CD8+ lymphocytes can be observed in autoimmune and allergic conditions. The coefficient of CD4+/CD8+ (immune correcting code) is higher than normal. Its indexes in healthy persons taken as regional norm, – are (1.59±0.08), reference values – (0.75±2.9). One cell of T-suppressors is for normal immune response to 2-3 cells of T-helpers [23].

According to the study results it was found that level of CD8+ lymphocytes depended on both the severity of COPD and on the presence of concomitant pathology or comorbidity. Possible increase of the number of CD8+ lymphocytes in patients with COPD exacerbation compared to the control group was determined. Thus, in patients with isolated COPD course the index of CD8+ T-cells was (26.2±2.08%) of the total population of lymphocytes, whereas in the control it was (23.9±3.16%) (p<0.05). In patients with COPD and concomitant SIHD this index was 1.12 times (p<0.05) more, and in patients with COPD in combination with comorbid IHD is also 1.18 times higher (p<0.05). This discrepancy in quantitative and relative terms in a subpopulation of CD8+ T-cells in isolated course of COPD and in CRP, according to many researchers is a compelling evidence of incoordination of the immune system in this cohort of patients [24, 25]. According to dissociation of the relative number of CD4+ and CD8+ lymphocytes in COPD, which is determined regardless of diseases syntrophy, decreased

immune-regulatory index (IRI) from (1.60±0.08) in patients with isolated COPD of the III[rd] degree course up to (1.38±0.06) and (1.02±0.08) in patients of the main group and subgroup of comparison were observed. IRI index in the second group of patients was the lowest due to increasing number of CD8+ cells (cytotoxic suppressors), indicating the existence of irregularities in relation of immune-regulatory subpopulations of T-lymphocytes in COPD. So, one of the pathogenic mechanisms of COPD and SIHD combination is the emergence of imbalance in the functioning and quantitative composition of T-cell immunity. In our view, the determined changes of CD4+ and CD8+ T-cells in peripheral blood of patients with exacerbation of COPD of the III[rd] degree is the prominent evidence of the disorder of lymphocytic cooperation and immune response. According to the results of previous studies, reduction of the absolute and relative number of CD3+ and CD4+ T-cells, to some extent, is due to the increased lymphocytic infiltration of the bronchial walls of patients in this category.

In the primary study the immunological deficiency of NK-cells (CD16+ lymphocytes) in patients with isolated course of COPD of the III[rd] degree of severity, level of which was (15.06±0.35%) and was lower 1.13 times compared to the control group (16.98±0.13%), (p>0.05), was determined. Indicators of subpopulation pool of CD16+ lymphocytes in patients with combined CRP were significantly lower compared with patients of the first group and the group of PHP (p<0.05 for both indicators) that led to the weakening of protection against infectious agents in early stages of the immune response. NK deficit correlated both with the severity of the underlying disease, and with the presence of the CRP. The received data coincide with the results of other scientists' research [26, 27].

It is proved that NK-cells play an important regulation of inflammatory process in various sites, including the bronchopulmonary complex, and are the main defenders of the organism from microorganisms in early stage of the immune response. Natural NK-cells express CD16+ markers, which are the receptors for part of the immunoglobulin molecule that determines the severity of humoral protection. Natural killer cells also play an important role in the elimination of tumour and virus-infected cells [21].

Exacerbation of COPD is accompanied by a decrease in levels of both absolute and relative number of CD22+ lymphocytes (mature B-lymphocytes) in patients with CRP. The most pronounced decrease in CD22+ lymphocytes was observed in patients with COPD combined with concomitant coronary artery disease, which was (20.2±0.67%); and in patients with comorbid CHD, respectively (19.96±0.43%) (p<0.01-p<0.001 for both indicators). Similarly, the rate of CD22+ lymphocytes in patients with isolated course of COPD of the III[rd] degree was significantly higher: 1.11 times compared to the PHP group (p<0.05), – 1.23 times (p<0.01) compared to the main subgroup, and 1.24 times (p<0.01) compared with group of comparison. It is known that CD22+ receptor belongs to the superfamily of immunoglobulins, function of which aims at linking of sialoconjugate and determination of the levels of production of immunoglobulins A, M, G and E in blood serum and circulating immune complexes in the blood and in response to RBTL on B-cellular mitogen (E. coli or S. typhimurium) [27].

Thus, the found violations in a population of T-cell immunity certify their severity in patients with COPD of moderate and severe course. Since lymphocytes of T-cellular immunity are directly related to the production of cytokines and cytokine expression imbalance, determining of their cellular structure and functional activity in patients with COPD is very important.

Conclusions

1. Study of indicators that characterize the cellular component of the immune response showed significant violations in patients with acute exacerbation of COPD of the III[rd] degree of severity, groups C and D showed the presence of immunodeficiency state.
2. Indexes of levels of certain subpopulations of lymphocytes depended on the severity of COPD and the presence of concomitant or combined cardiovascular disease.
3. In exacerbation of COPD of the III[rd] degree with concomitant or comorbid SIHD SAP I-II FC, changes in cellular link of immunity were observed; they were manifested by a decrease in the absolute and relative number of T-lymphocytes (predominantly helper failure), lack of natural killer cells and lymphocytes, which are responsible for the levels of production of immunoglobulins, indicating depression of T- and B-cell immunity links.

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