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Comparative Assessment of Clinical and Immunological Features of Chronic Obstructive Pulmonary Disease and its Combination with Covid-19

Mukumova SA. — Doctor's office, Samarkand branch of the Republican Scientific Center for Urgent Ambulance Samarkand Uzbekistan.

Madjidova G. T. – assistant at the Department of Internal Medicine No. 2 and Cardiology Samarkand State Medical University;

Sunnatova G. I. - assistant at the Department of Internal Medicine No. 2 and Cardiology Samarkand State Medical University;

Xaydarova D.D. - assistant at the Department of Internal Medicine No. 2 and Cardiology Samarkand State Medical University;

Mirzayev R.Z. - assistant at the Department of Internal Medicine No. 2 and Cardiology Samarkand State Medical University;

Annotation. _ The relevance of the problem of chronic obstructive pulmonary disease (COPD) is due to the prevalence of the disease, high mortality, high economic costs associated with the treatment of patients [1]. The development of inflammation in this disease and its prognosis are largely determined by the state of the immune system. Defects in the state of the immune system contribute to the persistence of the inflammatory process in the lungs, are a common cause of exacerbations of the disease, and reduce the effectiveness of the therapy [2]. As the severity of COPD increases in patients, the risk of developing community-acquired pneumonia (COVID-19 with pneumonia) increases, which is characterized by a protracted course and is often associated with a poor prognosis [3]. In turn, the transferred pneumonia in patients is a predictor of repeated exacerbations of COPD and deaths [4].

Based on this, it is of considerable scientific and practical interest to study the immunological mechanisms of inflammation in COPD and the comorbid course of COPD and COVID-19 with pneumonia.

The aim of the study is to study the features of the clinical picture and immune status in patients with chronic obstructive pulmonary disease and its combination with COVID-19 with pneumonia.

Material and methods. The study included 98 patients with COPD who received treatment in the city of Samarkand in the departments of a specialized center for combating COVID-19 and were divided into two groups. Patients with COPD exacerbation made up the first group (*n* =45), patients in whom the disease was combined with community-acquired pneumonia (COPD+COVID-19 with pneumonia) were included in the second group (n=43). The diagnosis of COVID-19 with pneumonia was established on the basis of epidemiological, laboratory, clinical and radiological data characteristic of this disease [5]. COPD was diagnosed based on the GOLD-2016 criteria [1].

The criteria for exclusion of patients from the study were tuberculosis, oncological diseases, bronchial asthma, blood diseases, hepatitis B and C, human immunodeficiency virus. The control group consisted of 30 practically healthy individuals. Assessment of the anamnesis of life and disease was carried out during hospitalization of patients. Analysis of the dynamics of treatment was carried out using clinical, laboratory and instrumental methods

of examination. We analyzed the data of chest radiography, pulse oximetry , and evaluated the function of external respiration (PFR). The prognosis of the disease and the choice of the place of treatment for patients with COPD+COVID-19 with pneumonia were assessed in accordance with the CRB-65 scale [6]. When analyzing clinical data in patients, the comorbidity index was calculated in points Charlson [7], the severity of dyspnea was assessed using the MRS scale (Modified British Medical Research Council) [8], the calculation of the cumulative index (CI) in points was performed using the scale of the severity of the main symptoms of COPD [9]. In the studied patients during treatment, the level of serum C-reactive protein (CRP), an inflammatory marker, was determined in the blood.

The immunological study included the determination of B-lymphocytes (CD19+), T-lymphocytes (CD3+), T-helpers (CD4+), natural killers (CD16+, CD56+), cytotoxic T-lymphocytes (CD8+) by flow cytometry using the Cytomics FC - 500 device » (Beckman Coulter , USA) [10], circulating immune complexes (CIC) [11] and immunoglobulins (Ig) of classes A, M, G in blood serum [12]. Using the method of enzyme-linked immunosorbent assay, the content of IL-6, TNF-α was determined. In addition, the phagocytic activity of blood neutrophils was studied by the ability to absorb latex particles with the determination of the phagocytic index (PI) and phagocytic number (PF) [13].

During the period of hospitalization, patients received standard treatment, including inhaled bronchodilators , antibacterial drugs , glucocorticoids (if indicated), oxygen therapy, symptomatic agents . between groups are significant at $p < 0.05$.

Results and its discussion. Demographic parameters in the studied patients did not differ significantly. These were male, current or former smokers with a long history of smoking, with the same experience of COPD *(Table 1).*

Table 1 Characteristics of patients included in the study

Options	Patients with COPD (*n* =4 5)	Patients with COPD+COVID-19 with pneumonia (*n* =4 3)
Average age, *years*	64.7±1.2	62.2±1.8
Average duration of COPD, *years*	6.4±0.4	4.7±0.7
Smokers/Non-smokers	23/8	11/10
Smoking experience, *pack/years*	47.03±2.5	43.8±1.8
Body mass index, *kg / m* 2	28.3±0.8	28.3±1.03
SpO2, %	97.5%±2.8	79.1%±2.1
CRP , *mg/l*	24.2±0.6	34.9±3.4*
CI, *points*	4.01±0.07	2.86±0.06*

Note : * p< 0.05 differences between groups of patients with COPD and patients with COPD+COVID-19 with pneumonia

The prognosis of the disease and the choice of the place of treatment for patients with COPD+COVID-19 with pneumonia were assessed according to the CRB-65 scale, the average score for which was 2.13±0.3. During hospitalization in patients with COPD, two or more signs of exacerbation according to NR Anthonisen were observed. et al [14].

When analyzing the clinical picture of the disease in patients included in the study, various concomitant diseases (IHD, hypertension, cerebrovascular diseases, diabetes mellitus, etc.) were identified. At the same time, the comorbidity index Charlson in patients with COPD+COVID-19 with pneumonia was higher than in patients with COPD ($p < 0.05$). Impaired lung function in COPD+COVID-19 patients with pneumonia was more pronounced. In them, the values of forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1) were (43.5±3.1)% and (26.1±2.5) % , respectively; in patients with exacerbation of COPD, these the indicators were higher and amounted to (56.7±2.5)% and (36.3±1.6)%, respectively ($p<0.05$). Clinically, this was manifested by varying degrees of dyspnea. Its intensity on the mMRS scale was higher in patients of the second group than in patients of the first group ($p < 0.05$). The development of respiratory failure in patients included in the study was accompanied by impaired blood oxygenation. SpO2 values in patients with COPD+COVID-19 with pneumonia and COPD were reduced compared to healthy controls [respectively (89.1±2.1)% and (91.5±2.8)% or

(97.6±1,4)%; p<0.05]. There were no significant differences in this parameter between groups of patients (p>0.05).

More significant changes were found for the serum CRP content, which is a marker of inflammation. In healthy individuals, the level of CRP in the blood averaged (4.08±0.1) mg/l. In patients included in the study, its level increased by an average of 5.6–8.3 times (p < 0.05). In patients of the second group, the content of serum CRP was significantly higher than in patients of the first group (p < 0.05), which indicates the presence of more intense inflammation in patients with COPD+COVID-19 with pneumonia.

In a comprehensive assessment of respiratory symptoms, their severity was higher in patients with COPD+COVID-19 with pneumonia. Their cumulative index (CI) was (2.96±0.06) points, while in patients with COPD it was (2.01±0.07) points (p< 0.05).

Thus, compared with patients of the first group, patients with COPD+COVID-19 with pneumonia have more pronounced clinical symptoms of the disease, impaired lung function, as well as higher comorbidity index and serum CRP levels.

During treatment, the severity of respiratory symptoms in patients decreased. CI values in patients with COPD+COVID-19 with pneumonia decreased to (1.57±0.07) points (p< 0.05), and in patients with COPD - to (1.26±0.05) points (p<0.05).

In patients with COPD, according to the mMRS scale , the severity of dyspnea decreased to (1.8±0.1) points, and in patients with COPD+COVID-19 WITH PNEUMONIA, to (2.3±0.1) points (p < 0, 05). Differences in the severity of dyspnea between groups of patients after treatment were statistically significant. In patients with COPD+COVID-19 WITH PNEUMONIA, there was an increase in functional parameters. The values of FEV 1 and FVC increased to (49.8±2.1)% and (30.4±1.9)% , respectively (p<0.05). The values of FVC and FEV1 in patients with COPD were not statistically significant [(59.1±2.1)% and (39.1±1.2)% (p>0.05)]. As follows from the presented data, more pronounced violations of FEV1 and FVC were observed in patients of the second group (p < 0.05).

During treatment, patients showed an improvement in SpO2 blood oxygenation. In patients with COPD+COVID-19 with pneumonia, SpO2 increased to (94.2±2.4)% (p<0.05), and in patients with COPD, respectively, to (93.1±2.5)% (p <0.05). There were no significant differences between the groups for this parameter (p>0.05).

The decrease in serum CRP in patients with COPD+COVID-19 with pneumonia occurred to an average value of (12.5±1.2) mg/l (p< 0.05), which was significantly higher than in patients with COPD - (8.2±0.9) mg/l (p<0.05).

An analysis of the results of an immunological study of patients included in the study showed the presence of various disorders in all parts of the immune system (Table 2).

In patients in the first group, exacerbation of the disease was accompanied by a decrease in the relative and absolute number of lymphocytes, mature T-lymphocytes (CD3+), T-helpers (CD4+) and NK cells (CD16+, CD56+) (p<0.05) . The level of cytotoxic T-lymphocytes (CD8+) in these patients did not differ from normal values. At the same time, the relative and absolute content of B-lymphocytes (CD19+) in patients with COPD was higher than in healthy people (p < 0.05).

In patients with COPD+COVID-19 with pneumonia during hospitalization, as in patients with COPD, the content of lymphocytes in the blood was reduced. However, compared with patients with COPD, they had lower relative and absolute numbers of CD3+-, CD4+-, CD8+- lymphocytes (p< 0.05). Also, in patients with COPD+COVID-19 with pneumonia, the relative and absolute number of NK cells was reduced (p < 0.05). But according to this indicator, there were no significant differences with patients with COPD (p>0.05). On the contrary, the relative and absolute content of B-lymphocytes (CD19+) in patients of the second group was higher than in patients of the first group (p < 0.05).

The presence of disorders in the state of humoral immunity in patients was evidenced by a decrease in serum IgA and IgG (p< 0.05), as well as an increase in IgM (p<0.05). At the same time, in patients of the second group, compared with patients of the first group, the content of IgM in the blood serum was higher [(1.97±0.05) g/l or (1.79±0.06) g/l; p< 0.05]. In patients of both groups, the CEC level was increased by an average of 2.8–3.2 times. There were no significant differences in the CEC level between the two groups of patients (p>0.05).

In the study of immunoregulatory substances in patients included in the study, an increase in the serum level of

pro-inflammatory cytokines: IL-6 and TNF-α ($p < 0.05$) was revealed. In patients with COPD, the content of IL-6 exceeded normal values by an average of 4.5 times, and TNF-α - by 2.4 times. In patients with COPD+COVID-19 with pneumonia, the content of these immunoregulatory substances was higher than in patients with COPD ($p < 0.05$).

The course of the disease in patients was accompanied by a violation of the phagocytic activity of blood neutrophils. Compared with healthy individuals, the studied patients showed a decrease in FI and PF ($p < 0.05$). Statistically significant differences in the values of FC and FI in patients of both groups were not detected ($p>0.05$).

Thus, in patients with COPD+COVID-19 with pneumonia, there were more pronounced disorders in cellular immunity, production of IgM and pro-inflammatory cytokines IL-6 and TNF-α.

As a result of the treatment in patients with exacerbation of COPD, the relative content of lymphocytes increased ($p < 0.05$) (see Table 2). Despite this, the relative and absolute number of CD3+ and CD4+ lymphocytes remained low ($p< 0.05$). During treatment, the absolute and relative number of NK cells in patients with COPD increased and reached normal values. In patients with COPD, there was a trend towards a decrease in the level of B-lymphocytes. However, the content of CD19+ cells was significantly higher than in healthy people ($p< 0.05$).

In the studied patients, after the therapy, the relative content of lymphocytes remained low (see Table 2). The number of CD3+-, CD4+-, CD8+-cells in patients with COPD+COVID-19 with pneumonia increased, but was lower than in healthy individuals ($p< 0.05$).

There were no significant differences in the content of CD3+-, CD4+-, CD8+-lymphocytes between the groups of patients ($p>0.05$). In patients with COPD+COVID-19 with pneumonia, there was a decrease in the relative and absolute number of CD16+-, CD56+- and CD19+-lymphocytes. At the same time, in these patients, the level of B-lymphocytes was higher, and the number of NK cells, respectively, was lower than in healthy individuals and patients with COPD ($p < 0.05$).

In patients in both selected groups, the content of IgA increased , there was a tendency to a decrease in IgM . However, the IgM level in patients with COPD+COVID-19 with pneumonia was higher than in healthy individuals and patients with COPD ($p < 0.05$). The content of IgG in patients in both groups remained low.

Moreover, in patients with COPD+COVID-19 with pneumonia, IgG levels after treatment were lower than in patients with COPD ($p < 0.05$). In the dynamics of observation in patients in both groups, there was a decrease in the CEC. However, the level of CEC in their blood was higher than the control values. There were no significant differences between the two groups of patients in this parameter ($p>0.05$).

It should be noted that by the end of the course of treatment in patients in both groups, the content of IL-6 in the blood serum increased ($p < 0.05$). The level of TNF-α in patients with COPD and COPD+COVID-19 with pneumonia was without dynamics high. In patients with COPD+COVID-19 with pneumonia, compared with patients with COPD, the content of pro-inflammatory cytokines was significantly higher ($p < 0.05$).

The phagocytic activity of blood neutrophils in patients with COPD and COPD+COVID-19 with pneumonia practically did not change and remained low. Statistical difference in the values of FC and FI of blood neutrophils in patients of the first and second groups was not detected ($p>0.05$).

Thus, in patients with COPD+COVID-19 with pneumonia, more pronounced symptoms of the disease and impaired immune status persisted after the therapy.

Discussing the obtained data, it should be taken into account that in the development of immunological disorders in patients, an important role belongs to age characteristics, exposure to various stimuli, the duration of the disease, the presence of comorbid conditions, and ongoing drug therapy [15]. Considering from these positions the patients included in this study, it can be noted that they were people of older age groups, tobacco smokers with a long history of chronic lung disease and other concomitant diseases. In the basic therapy of the underlying disease of COPD, these patients took various medications. In turn, immunological disorders that occur in patients with COPD can lead to the formation of a vicious circle and cause the progression of the inflammatory process.

Conclusions:

1. Patients with COPD+COVID-19 with pneumonia have higher intensity of respiratory symptoms, comorbidity index and blood CRP levels, lower spirometric parameters compared to patients with exacerbation of COPD.
2. The course of the disease both in patients with COPD+COVID-19 with pneumonia and in patients with exacerbation of COPD is accompanied by immunological disorders. Compared to COPD patients, patients with COPD+COVID-19 with pneumonia have reduced T- helper and T- suppressor cell activity, increased levels of B-lymphocytes, IgM , IL-6, and TNF-α.
3. After treatment, in patients with COPD+COVID-19 with pneumonia, clinical symptoms and manifestations of systemic inflammation remained more pronounced, the content of NK-cells and IgG remained low , and the level of CD19+-lymphocytes, IgM and pro-inflammatory cytokines remained high.

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