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Th1/Th17 Cytokines of the Immune Response in Patients with Bronchial Asthma after COVID-19

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ABSTRACT

Aim. To study the content of interleukin 1β (IL-1β) in exhaled breath condensate (EBC) and interleukin 6 (IL-6) and 17A (IL-17A) in the blood serum of patients with bronchial asthma who experienced COVID-19 of varying severity.

Materials and methods. We examined 124 adult asthma patients of both sexes 6–12 months after COVID-19. The design included a general examination to determine the objective status of patients, asthma severity and control, assessment of the lung function, and measurement of IL-1β in EBC and IL-6, IL-17A in the serum of peripheral blood.

Results. The patients were divided into 2 groups. Group 1 consisted of 90 patients with mild persistent asthma. Group 2 included 34 patients with moderate asthma. The content of IL-6 and IL-17A in the blood serum of patients in group 1 was significantly lower than in group 2 ($p = 0.047$ and $p = 0.049$, respectively). The concentration of IL-1β in the EBC of patients in group 1 was significantly higher than in group 2 ($p = 0.019$). COVID-19-associated pneumonia was experienced by 40% of patients in group 1 and by 79% of patients in group 2. Post-COVID pulmonary fibrosis was registered in 19 and 62% of cases, respectively. In group 1, a relationship was revealed between the content of IL-17A and IL-6 in the blood ($Rs = 0.69$; $p < 0.001$). In group 2, a correlation was found between the content of IL-17A and IL-6 in the blood ($Rs = 0.32$; $p = 0.025$), as well as between the forced expiratory flow at 75% of forced vital capacity (FEF_{75}), reflecting the patency of small bronchi, and the levels of IL-6 ($Rs = –0.32$; $p = 0.023$) and IL-1β ($Rs = 0.49$; $p = 0.021$).

Conclusion. In patients who experienced COVID-19, a rise in the content of Th1/Th17 cytokines was observed as the severity of asthma increased. High concentrations of IL-17A and Th17-associated IL-1β and IL-6, which activate neutrophilic inflammation, may increase the risk of systemic inflammation and the development of pulmonary fibrosis.

Keywords: bronchial asthma, COVID-19, cytokines IL-1β, IL-6, and IL-17A, Th1/Th17-induced inflammation.

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Conformity with the principles of ehtics. All patients signed an informed consent to participate in the study. The study was approved by the local Ehtics Committee at Far Eastern Scientific Center of Physiology and Pathology of Respiration (Minutes No. 137 dated May 24, 2022).

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Цитокины Th1/Th17 иммунного ответа у больных бронхиальной астмой после перенесенной коронавирусной болезни 2019

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РЕЗЮМЕ

Цель. Исследовать содержание интерлейкина *(IL) 1β в конденсате выдыхаемого воздуха (КВВ) и IL-6, IL-17A в сыворотке крови* у пациентов с бронхиальной астмой (БА), переболевших коронавирусной болезнью 2019 (coronavirus disease 2019, COVID-19) разной степени тяжести.

Материалы и методы. Взрослые пациенты с БА (n = 124) обоего пола обследованы спустя 9–12 мес после перенесенной COVID-19. Дизайн предусматривал общий осмотр с определением объективного статуса больных, степени тяжести БА, уровня контроля над болезнью, оценку вентиляционной функции легких, измерение содержания IL-1β в КВВ и IL-6, IL-17A в сыворотке периферической крови.

Результаты. Больные распределены на две группы: 1-ю группу составили 90 пациентов с легкой персистирующей БА, 2-ю группу – 34 пациента со среднетяжелой БА. Содержание IL-6 и IL-17A в сыворотке крови пациентов 1-й группы было достоверно ниже, чем во 2-й (p = 0,047 и p = 0,049 соответственно). Концентрация IL-1β в КВВ у пациентов 1-й группы была существенно выше, чем во 2-й группе (p = 0,019). В 1-й группе 40% больных и 79% во 2-й перенесли COVID-19-ассоциированную пневмонию. Постковидный пневмофиброз зарегистрирован в 19 и 62% случаев соответственно. В 1-й группе прослеживалась взаимосвязь между содержанием IL-17A и IL-6 в крови (Rs = 0,69; p < 0,001), во 2-й группе – между содержанием IL-17A и IL-6 в крови (Rs = 0,32; p = 0,025), а также между максимальной объемной скоростью на уровне 75% форсированной жизненной емкости легких ($МОС_{75}$), отражающей проходимость мелких бронхов, и уровнем IL-6 (Rs = –0,32; p = 0,023) и IL-1β (Rs = 0,49; p = 0,021).

Заключение. У пациентов, перенесших COVID-19, по мере нарастания степени тяжести БА наблюдалось увеличение содержания цитокинов Th1/Th17. Высокие концентрации IL-17A и Th17-связанных IL-1β и IL-6, активирующих нейтрофильное воспаление, могут повышать риск системного воспаления и развития пневмофиброза.

Ключевые слова: бронхиальная астма, COVID-19, цитокины *IL-1β, IL-6 и IL-17A,* Th1/Th17-индуцированное воспаление

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

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INTRODUCTION

Studies investigating the cooccurrence of bronchial asthma (BA) and COVID-19 have shown that older age, a large number of comorbidities, as well as eosinopenia and lymphopenia significantly increase susceptibility to SARS-CoV-2 infection [1]. It is hypothesized that diabetes mellitus and hypertension may upregulate the expression of angiotensin-converting enzyme 2 (ACE2), whereas the use of inhaled corticosteroids contributes to its downregulation, thereby hindering SARS-CoV-2 entry into the epithelium [2]. Significant factors for mortality among patients with COVID-19 and BA include a history of asthma exacerbation

within a year prior to COVID-19 and an increase in asthma severity [3].

Of particular note is the increased susceptibility to SARS-CoV-2 in patients with non-allergic BA. This phenotype is frequently associated with severe COVID-19, necessitating intensive care, mechanical ventilation, and / or leading to a fatal outcome [4, 5]. This observation can be explained by higher ACE2 expression levels in these patients compared to those with the allergic asthma phenotype [6, 7].

The critical course of COVID-19, driven by the cytopathic effect of SARS-CoV-2 on target cells expressing ACE2 receptors and coreceptors – transmembrane serine protease TMPRSS2 and cathepsin L – leads to the release of damage-associated molecular patterns (DAMPs) and is accompanied by the induction of cellular pyroptosis. The generation of numerous inflammatory mediators, neutrophil activation with the formation of neutrophil extracellular traps (NETs) that contribute to lung epithelial cell death, the development of macrophage activation syndrome (MAS), hyperinflammation, and cytokine storm are all associated with the overproduction of IL-1β, IL-6, and IL-17 among other proinflammatory cytokines [8–10]. In patients with non-allergic BA, IL-1β, IL-6, and IL-17 act as central regulators of Th2/Th17 or Th1/Th17 inflammatory patterns with predominant bronchial neutrophilic infiltration [11]. Severe uncontrolled non-atopic asthma is dominated by a Th1/Th17 immune response and increased production of proinflammatory cytokines in the airways, which modify the respiratory tract structure, potentiate remodeling and bronchial obstruction, and cause a decrease in forced expiratory volume in 1 second (FEV_1) [12, 13].

Since IL-1β, IL-6, and IL-17 are key players in systemic inflammation and complications of COVID-19, as well as in the Th1/Th17 immune response in BA, profiling these cytokines in patients with both diseases holds significant prognostic value.

The aim of the study was to investigate the levels of IL-1β in exhaled breath condensate and the levels of IL-6 and IL-17A in serum in patients with BA of varying severity who recovered from COVID-19.

MATERIALS AND METHODS

A total of 124 adult patients with BA were enrolled in a single-center, observational, cross-sectional, cohort study 9–12 months after a confirmed COVID-19 infection. The diagnosis of BA was based on the ICD-10 codes and the GINA criteria [14].

A prior COVID-19 infection was confirmed using medical records, which documented the verification of SARS-CoV-2 RNA in oropharyngeal and / or nasopharyngeal swab specimens by nucleic acid amplification tests or the detection of SARS-CoV-2 antigen by the immunochromatographic assay. The COVID-19 diagnosis was established according to the version of the temporary methodological guidelines of the Russian Ministry of Health "Prevention, Diagnosis, and Treatment of Novel Coronavirus Infection (COVID-19)" that was in effect at the time of the patient's examination.

Clinical material was collected in 2022–2023 during patient visits at the Far Eastern Scientific Center of Physiology and Pathology of Respiration. The study was approved by the local Ethics Committee at this Scientific Center (Minutes No.137 dated May 24, 2022).

Inclusion criteria were the following: adult individuals of both sexes; diagnosis of BA corresponding to the ICD-10 codes J45.1, J45.8, J45.9, persistent mild and moderate BA; a history of COVID-19 of varying severity, confirmed by laboratory methods; presentation for the study 9–12 months after the completion of COVID-19 therapy; ability to technically correctly perform maneuvers during instrumental testing; a written informed consent to the examination.

Exclusion criteria: BA corresponding to the ICD-10 code J45.0, severe BA; presence of comorbid pathology and drug therapy that could lead to distortion of the results of the collected biological material analysis; lack of interest or failure to provide a written informed consent.

Study design: patient selection at the stage of presentation to the Far Eastern Scientific Center of Physiology and Pathology of Respiration; general examination with assessment of the objective status, asthma severity, and level of disease control; evaluation of lung function; collection of biological fluids – peripheral blood and exhaled breath condensate (EBC).

Following the completion of sample collection, the patients were divided into groups based on disease severity: group 1 included 90 individuals with mild persistent BA, and group 2 comprised 34 patients with moderate disease severity. The main clinical characteristics of the examined patients are presented in Table 1.

BA symptoms were objectively assessed using the validated questionnaires Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ-5).

Table 1

Main Clinical Parameters of Patients with Bronchial Asthma

Parameter	Group 1	Group 2	*p*
Age, years, *Me* [Q_1; Q_3]	42[31;53]	50[49;65]	<0.001
BMI, kg/m², *Me* [Q_1; Q_3]	26.6[23.2;30.5]	29.3[26.1;32.7]	0.007
Sex (male/female), %	49/51	44/56	>0.05
Proportion of smokers, %	22	38	<0.05; $\chi^2 = 4.6$
Smoking, pack – years, *Me* [Q_1; Q_3]	12[5;20]	17[3;30]	>0.05
ACT score, *Me* [Q_1; Q_3]	18[15;21]	12[10;13]	0.002
ACQ-5 score, *Me* [Q_1; Q_3]	2.0[1.0;3.0]	2.8[2.4;3.2]	0.057
SaO_2, %, *Me* [Q_1; Q_3]	97[96;98]	96[94;97]	<0.001
IgE, IU/ml, *Me* [Q_1; Q_3]	32[13;74]	160[48;266]	<0.001

Note. BMI – body mass index; ACT – Asthma Control Test; ACQ-5 – Asthma Control Questionnaire-5; SaO_2 – oxygen saturation; IgE – immunoglobulin E, *p* – the significance level for differences between group 1 and group 2 (here and further).

Lung function was evaluated by spirometry using the Easy on-PC electronic spirometer (ndd Medizintechnik AG, Switzerland) equipped with an ultrasonic flow sensor based on ndd True Flow™ technology. The measured parameters included forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), maximum forced expiratory flow at 50% and 75% of FVC (FEF_{50} and FEF_{75}, respectively), and mid-expiratory flow between 25% and 75% of FVC (MEF_{25-75}). The measurement and analysis of the recorded parameters followed the methodological guidelines for conducting studies and interpreting results and quality standards recommended by the Russian Respiratory Society, which are in line with the standards of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) [15, 16]. The patient's actual values were expressed as a percentage of predicted values based on the European Community for Steel and Coal (ECSC) reference values for individuals over 18 years. Reversibility of obstructive abnormalities was assessed via a bronchodilation test using a short-acting β_2-agonist (salbutamol 400 mcg) [15].

Additionally, patients in group 1 with FEV_1 greater than 75% underwent a bronchoprovocation test with 3-minute isocapnic cold air hyperventilation (–20 °C) to verify cold air hyperresponsiveness [17].

EBC samples were collected using the ECoScreen II device (VIASUS Healthcare GmbH, Germany). Collection was performed once before noon or sequentially before and after the cold air hyperventilation challenge test. Prior to the procedure, the patients rinsed their oral cavity twice with distilled water. Subsequently, while breathing calmly through a mouthpiece for 20 minutes, they ventilated air through the device, with nasal breathing occluded by a nose clip. Upon completion, the container with the biological material was removed from the device. Following thawing, the liquid condensate was aliquoted in 1000-μl volumes into sterile 1.5 ml Eppendorf-type plastic tubes using a Light DPOP-1-100-1000 single-channel pipette dispenser (Thermo Scientific). The tubes were sealed with airtight caps and immediately placed in a freezer at approximately –80 °C, where they were stored for no more than two weeks until biochemical analysis. The concentration of IL-1β (in pg/ml) in the EBC was determined using commercial LEGENDplex™ Human T Helper Cytokine Panel Version 2 kits on a FACS Canto II flow cytometer (Becton Dickinson, USA) with the FACS Diva 6.0 software (Becton Dickinson, USA).

Peripheral blood was collected once from the median cubital vein in the morning (before 9:00 AM). A 2 ml-volume of venous blood was drawn into vacuum tubes containing a coagulation activator, incubated for 30 minutes at room temperature, and subsequently centrifuged at 3,000g for 10 minutes at 4 °C. The obtained serum was stored at –20 °C until analysis. Cytokine concentrations of IL-6 and IL-17A (pg/ml) were measured using commercial LEGENDplex™ Human T Helper Cytokine Panel Version 2 kits on a FACS Canto II flow cytometer (Becton Dickinson, USA) with the FACS Diva 6.0 software (Becton Dickinson, USA).

Statistical analysis was performed using the Automated Medical Examination System software (Russia) [18]. The normality of distribution was assessed using the Kolmogorov – Smirnov test, the Pearson – von Mises test, and measures of skewness and kurtosis. For comparing two independent samples, the Student's *t*-test was applied when data followed a normal distribution and group variances were homogeneous according to the Fisher's test; otherwise, the Mann – Whitney *U*-test or Kolmogorov – Smirnov test was used. For comparing two dependent samples, the Wilcoxon signed-rank test was employed. Quantitative parameters were presented as either $M \pm SD$ (where *M* is the arithmetic mean and *SD* is

the standard deviation) or as $Me[Q_1;Q_3]$ (where *Me* is the median and Q_1–Q_3 is the interquartile range). Frequencies of categorical variables were analyzed using the χ^2 (Pearson›s chi-squared) test. Correlation between two random variables was determined using the Spearman's nonparametric correlation analysis (*Rs*). The differences were considered to be statistically significant at $p < 0.05$.

RESULTS

Analysis of the blood cytokine profile involved in the Th1/Th17 immune response in BA patients revealed significantly higher levels of IL-6 and IL-17A in group 2 compared to group 1 (Table 2). In the meantime, group 2 showed significantly lower levels of IL-1β in EBC than group 1 (Figure). Notably, in patients who underwent the cold air challenge test, IL-1β levels increased after the test, suggesting the active role of the cytokines in mediating the acute response to cold air bronchoprovocation (Table 2).

This finding is consistent with our previous research, which demonstrated an association between IL-1β and the non-atopic asthma phenotype, cold air hyperresponsiveness, and the probable development of a Th1/Th17 immune response, regulated by this cytokine [19].

Table 2

Levels of IL-6 and IL-17A in Peripheral Blood of Asthma Patients, pg/ml, *Me* [Q_1; Q_3]

Parameter	Group 1	Group 2	*p*
IL-6	6.70 [5.10;11.92]	10.20 [5.40;17.60]	0.047
IL-17A	0.14 [0.04;0.36]	0.28 [0.18;0.46]	0.049

The assessment of clinical and functional data revealed that patients in group 2 had poorer disease control compared to those in group 1 (Table 1). Both groups demonstrated low median ACT scores. In group 1, asthma was newly diagnosed in 60% of patients and required therapeutic intervention. Poor disease control was observed in 16% of cases, while only 24% of individuals exhibited partially controlled disease. Bronchospasm in response to cold air inhalation during the isocapnic hyperventilation challenge was detected in 36% of group 1 patients. In group 2, asthma exacerbation was present in 50% of cases, with uncontrolled disease, in 30% of cases and with partially controlled disease, in only 20%. Notably, COVID-19-associated pneumonia was reported in 40% of group 1 and 79% of group 2 patients. According to multispiral computed tomography results, bilateral post-COVID pulmonary fibrosis with polysegmental distribution

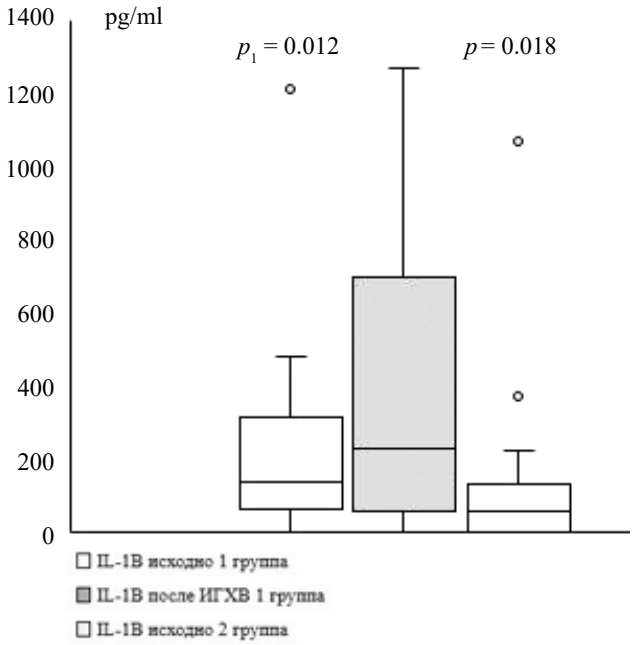

Fig. Level of IL-1β in exhaled breath condensate, pg/ml: *p* – significance level for the differences (Mann – Whitney *U*-test) between group 1 and group 2; p_1 – significance level for the differences (Wilcoxon signed-rank test) between group 1 patients before and after the isocapnic cold air hyperventilation challenge.

was documented in 62% of group 2 patients. Foci of pulmonary fibrosis were also observed in 19% of group 1 patients.

Comparison of key flow – volume curve parameters (FEV_1, FEV_1/FVC) and distal airway patency (FEF_{50}, FEF_{75}, MEF_{25-75}) indicated significantly worse lung function in group 2 patients compared to group 1 (Table 3).

Table 3

Flow – volume Curve Parameters of Forced Expiration and Changes in FEV_1 (ΔFEV_1bd) after Short-acting β_2-agonist Inhalation, *M* ± *SD*

Parameter	Group 1	Group 2	*p*
FEV_1, % predicted	94.3 ± 11.4	71.1 ± 22.2	<0.001
FEV_1/FVC, %	74.7 ± 7.6	64.9 ± 9.9	<0.001
FEF_{50}, % predicted	62.0 ± 33.2	42.8 ± 20.4	<0.001
FEF_{75}, % predicted	51.0 ± 30.3	35.7 ± 17.5	<0.001
MEF_{25-75}, % predicted	58.0 ± 27.5	41.2 ± 18.7	0.007
ΔFEV_1bd, %	7[3;12]	17[3;23]	0.004

Despite mean group values for FEV_1 and FEV_1/FVC in mild BA patients falling within the normal range, individual analysis revealed that 18% of patients had FEV_1 below 80% of the predicted value and the FEV_1/FVC ratio below 0.7. Furthermore,

isolated small airway obstruction was observed in 17% of patients. High bronchial lability (ΔFEV_1bd), exceeding 12% in the salbutamol test, was identified in 27% of group 1 and 57% of Group 2 patients. Two patients exhibited a paradoxical response to the short-acting bronchodilator, with FEV_1 decreasing by 11 and 30%, respectively.

The correlation analysis revealed significant associations between cytokine levels in EBC and serum and impaired lung function. In group 1, significant correlations were observed between serum IL-17A levels and bronchial response (ΔFEV_1) to the cold air hyperventilation challenge ($Rs = –0.40$, $p = 0.047$), serum IL-17A and IL-6 levels ($Rs = 0.69$, $p < 0.001$). In group 2, in addition to the positive correlation between serum IL-17A and IL-6 levels ($Rs = 0.32$, $p = 0.025$) that was also present in group 1, significant correlations were found between small airway patency (FEF_{75}) and IL-6 ($Rs = –0.32$, $p = 0.023$) and IL-1β levels ($Rs = 0.49$, $p = 0.021$).

DISCUSSION

Our findings suggest that IL-1β-induced synthesis of type 17 cytokines (IL-17A and IL-17F), whose primary function is neutrophil recruitment and activation, promotes the mobilization of the neutrophilic component in non-Th2-mediated asthma inflammation [20, 21]. As several authors contend, IL-1β plays a leading role in polarizing CD4+ T cells into the CD4+ T-helper 17 (Th17) subset, with IL-6 serving to amplify this process [22]. Furthermore, IL-1β-dependent IL-17 production is associated with the stimulation of innate immune cells belonging to specific minor subpopulations –namely, γδ T cells and group 3 innate lymphoid cells (ILC3s). These cells emerge during the immune response to pathogen invasion and possess the ability to produce IL-17 to maintain immune homeostasis, particularly in mucosal tissues [23].

According to another perspective, IL-1β further amplifies the function of IL-6, which is crucial for Th17 differentiation [24]. By inducing the expression of the key Th17 transcription factor RORγt and the related RORα in naive CD4+ T (T_0) cells, the content of which is associated with STAT3 activity, IL-6, acting via tyrosine residues of the signal transducer (subunit of the IL-6 receptor) gp130, activates STAT3 [25]. Activation of the IL-6 – gp130/STAT3 signaling pathway is considered as an IL-6/STAT3-dependent mechanism of pulmonary neutrophilic inflammation, making its components promising therapeutic targets in BA [26].

Neutrophilic inflammation is most frequently associated with elevated levels of IL-17A, the primary effector chemoattractant for neutrophils produced by the Th17 lineage. IL-17A is expressed by Th17 cells, and ILC3s are considered as a risk factor for the development of severe asthma [21, 27]. Key proinflammatory IL-17A-related cytokines and chemokines associated with activation of the transcription factor NF-κB — which is critical for the development of chronic airway inflammation — include IL-6, IL-1β, IL-8, and GM-CSF [23]. GM-CSF enhances neutrophil survival, adhesion, migration, and phagocytosis, promotes NET formation, stimulates the secretion of IL-6 and IL-23 by monocytes / macrophages, and participates in the expression of RORγt (necessary for Th17 cell differentiation) and CCL17/TARC, a key chemokine for recruiting these cells to the airways [23, 28, 29].

Our study revealed a strong association between BA severity and impaired lung function with elevated levels of serum IL-17A and its functionally related cytokine IL-6, both of which were significantly higher in the group of patients with moderate BA. It is reasonable to suggest the involvement of IL-17A and IL-6 in this disease phenotype, potentially mediated through neutrophil recruitment to the airway inflammatory infiltrate driven by increased production of these cytokines. This finding is supported by multiple publications demonstrating correlations between increased neutrophilic infiltration in the bronchi and elevated IL-17A levels in sputum, bronchoalveolar lavage fluid, and bronchial biopsy specimens (including epithelial cells, the subepithelial mucosal layer, and leiomyocytes) from patients with moderate-to-severe non-atopic steroid-resistant BA [13, 21, 27].

Previous studies have demonstrated a direct correlation between the number of Th17 cells in peripheral blood, sputum, and bronchoalveolar lavage fluid and the severity of airway remodeling in BA patients [24]. The elevated levels of IL-17A and IL-6 observed in group 2 patients, accompanied by probable escalation of bronchial inflammation through potential neutrophil mobilization and synthesis of proinflammatory cytokines, may adversely affect bronchial barrier function and stimulate airway remodeling, thereby worsening BA severity. BA severity is a factor that can exacerbate the infectious process following SARS-CoV-2 infection. Moderate-to-severe asthma is considered as a predictor of poor COVID-19 prognosis, with evidence indicating

a significantly higher mortality rate among these patients compared to those with mild disease (13.8% vs. 5.5%, $p = 0.006$) [3].

Based on multispiral computed tomography findings, we identified a substantial number of patients with post-COVID pulmonary fibrosis, particularly among those with moderate BA. These fibrotic changes in lung tissue should be considered in the context of the development and outcome of polymorphonuclear inflammation permeated by disintegrating neutrophils, resulting from the organization of exudative pneumonia foci caused by SARS-CoV-2. It is plausible that pre-existing neutrophilic airway inflammation in asthma patients — mediated by activation of Th1/Th17 immune response cytokines prior to SARS-CoV-2 infection — could have contributed to more severe lung damage during COVID-19.

The significance of neutrophilic infiltration as a key structural component of exudative pneumonia is supported by autopsy data from COVID-19 fatalities [30]. Microscopic examination of lung tissue in most cases revealed pronounced infiltration of interalveolar septa by neutrophils and mononuclear cells. Alveolar lumens, lined by hyaline membranes, contained abundant fibrinopurulent exudate rich in macrophages. Reactive hyperplasia and desquamation of alveolar epithelium were observed, along with thrombosis and hyalinosis of blood vessels in the pulmonary interstitium, fibroblast proliferation, and features of acute suppurative bronchiolitis with destruction and metaplasia of the bronchiolar epithelium.

Neutrophilia, along with eosinopenia, lymphopenia, and elevated levels of C-reactive protein in peripheral blood, has been identified among potential predictors of pulmonary fibrosis and long-term deterioration of lung function in COVID-19 patients. Other indicators associated with the risk of fibrotic remodeling and abnormal residual lung function include: patient age, severity of SARS-CoV-2 infection combined with chronic internal organ diseases, duration of intensive care unit stay for hospitalized patients, mechanical ventilation, and markers of hyperinflammation [31].

Assuming that BA patients had elevated concentrations of IL-1β, IL-6, and IL-17A prior to COVID-19, it is highly plausible that these cytokines contributed to the SARS-CoV-2-initiated lung injury, pneumonia, and hyperinflammation. In severe COVID-19, the cytopathic effect of SARS-CoV-2 triggers the release of damage-associated molecular patterns (DAMPs) from target cells. Released surface glycoproteins, ATP, and nucleic acids are recognized by neighboring epithelial cells, endothelial cells, and macrophages, stimulating pyroptosis — a highly inflammatory form of programmed cell death accompanied by IL-1β overproduction. Defects in apoptosis, caused by reduced cytolytic activity of NK cells and CD8+ T lymphocytes, may prolong the survival of virus-infected cells, leading to the accumulation of hyperactivated immune cells in the lungs and prolonged interaction between innate and adaptive immune cells. This cascade results in the generation of proinflammatory cytokines, cytokine storm, and the development of macrophage activation syndrome (MAS) [8, 10]. IL-1β and IL-6 serve as key inducers of hyperinflammation and MAS, which manifests as activation, uncontrolled expansion, and persistence of macrophages; massive cytokine secretion; induction of their synthesis by myeloid cells; hemophagocytosis; fibrinolytic coagulopathy; and multiorgan failure [10, 32]. Pathogenetic mechanisms predisposing to MAS include neutrophil hyperactivation, driven by the recruitment of granulocytes to the inflammation site via attractants, such as IL-7, IL-8, IFNγ, IP-10, as well as IL-1β, IL-6, and IL-17 from the Th1/Th17 subset. Neutrophil degranulation and the formation of abundant NETs promote inflammation escalation, damage to the vascular endothelium of the lungs and internal organs, and the development of microthromboses. NETs induce macrophage expression of IL-1β — a key mediator of MAS — which, in turn, activates pulmonary neutrophilic infiltration, neutrophilia, and NET formation [9, 10].

Thus, Th1/Th17-dependent activation of the neutrophilic component in the chronic airway inflammatory infiltrate of BA patients most likely contributes to the exacerbation of acute lung injury during COVID-19, laying the foundation for subsequent fibrotic replacement of respiratory tissue.

CONCLUSION

In asthma patients who have recovered from COVID-19, disease severity is associated with increased levels of Th1/Th17 cytokines in the blood. In mild BA, elevated IL-1β levels in exhaled breath condensate may be explained by its involvement in regulating the Th1/Th17 immune response and its contribution to cold air hyperresponsiveness. In contrast, patients with moderate BA demonstrated increased production of IL-6 and IL-17A, which was associated with impaired small airway patency, poor disease control, and likely activation of neutrophilic airway inflammation. Elevated concentrations of IL-

17A and related Th17 cytokines (IL-1β and IL-6) may increase the risk of systemic inflammation and pulmonary fibrosis development.

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