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CYTOKINE PROFILE OF BRONCHOALVEOLAR SECRETION IN PROLONGED COURSE OF COMMUNITY ACQUIRED PNEUMONIA

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Ключевые слова: *внебольничная пневмония, осложнения, бронхоальвеолярный секрет, цитокины*

Abstract. Cytokine profile of bronchoalveolar secretion in prolonged course of community acquired pneumonia. Razumniy R.V. *Despite existing studies on pathogenetic role of cytokine (CK) system in lung damage in pneumonia, there are still controversial issues of cytokine-mediated processes that lead to the prolongation of the inflammatory process in lung tissue in this pathology. The article presents the study of the cytokine profile of bronchoalveolar secretion (BAS) in the prolonged course of community-acquired pneumonia (CAP). To achieve the purpose of the research, in patients with prolonged CAP on the first and last 1-2 days of hospital stay the concentration of pro-inflammatory (IL-1β, IL-2, TNFα, IL-6, IL-8) and anti-inflammatory CK (IL-4 and IL-10) in BAS was determined. When studying the cytokine profile of BAS in the acute period of CAP, it was found that patients with a prolonged course of the disease subsequently had an increase in the concentration of pro-inflammatory CK (IL-1β, IL-6, IL-8, TNF-α and IL -2), reduction of anti-inflammatory (IL-4, IL-10) and more significant disproportion of the ratio of their opposition pools (IL-1β/IL-10 and TNF-α/IL-10) in BAS. In the conditions of the generally accepted therapy in patients with prolonged and not prolonged CAP course, various rate of improvement of indicators of CK in BAS is defined. In patients with prolonged CAP, the rate of progress of pro-inflammatory and anti-inflammatory CK was slower. At the time of discharge from the hospital, most patients had an imbalance of pro-inflammatory and anti-inflammatory CK with a predominance of pro-inflammatory activity in the bronchoalveolar space.*

Реферат. Цитокіновий профіль бронхоальвеолярного секрету при затяжному перебізі негоспітальної пневмонії. Разумний Р.В. *Незважаючи на існуючі дослідження щодо патогенетичної ролі системи цитокінів (ЦК) у пошкодженні легенів при пневмонії, до теперішнього часу залишаються дискусійними питання цитокінопосередкованих процесів, які призводять до пролонгації запального процесу в легеневій тканині при цій патології. Отже, у статті наведені результати дослідження цитокінового профілю бронхоальвеолярного секрету (БАС) при затяжному перебізі негоспітальної пневмонії (НП). Для реалізації мети цього дослідження хворим із затяжним перебігом НП у перші та останні 1-2 дні перебування в стаціонарі в БАС визначали концентрацію прозапальних (ІЛ-1β, ІЛ-2, ФНПα, ІЛ-6, ІЛ-8) та протизапальних ЦК (ІЛ-4 та ІЛ-10). При вивченні цитокінового профілю БАС у гострому періоді НП було встановлено, що у хворих, у яких в подальшому спостерігався затяжний перебіг захворювання, у БАС реєструвалося збільшення концентрації прозапальних ЦК (IL-1β, IL-6, IL-8, TNF-α та IL-2), зниження протизапальних (IL-4, IL-10) та більш істотна диспропорція співвідношення їх опозиційних пулів (IL-1β/IL-10 та TNF-α/IL-10). В умовах загальноприйнятої терапії у хворих із затяжним і не пролонгованим перебігом НП визначено різний темп покращення показників ЦК БАС. У хворих із затяжним перебігом НП темп поліпшення вмісту прозапальних та протизапальних ЦК був більш повільним і на момент виписки зі стаціонару в більшості пацієнтів зберігався дисбаланс прозапальних і протизапальних ЦК з превалюванням у бронхоальвеолярному просторі прозапальної активності.*

Nowadays, there is evidence of pathogenetic role of cytokines (CK) in respiratory diseases that have imbalances in this system [8, 10, 11]. However, despite the intensive studies, lung damage in pneumonia has a lot of controversial issues of cytokine-mediated processes that lead to the prolongation of the inflammatory process in the lung tissue in this pathology. In particular, it is believed that early hyperproduction of pro-inflammatory CK TNF-α and anti-inflammatory interleukin IL-10 on the background of depression markers of cell-mediated immune defence (IL-2, INFy) leads to a sharp increase in oxygen radicals and nitric oxide concentrations, the predominance of apoptosis over activation markers and contributes to the unfavourable course of pneumonia [4]. Other researchers indicate that low TNF-α and IL-1 correlate with phagocytic disorders, contributing to the dissemination of infection [12]. The correlation is recorded between the concentration of pro-and anti-inflammatory CK, and it depends on the etiological factor [5] and pneumonia severity [6, 7]. That is why in-depth study of the CK system and the analysis of the cytokine response heterogeneity will expand the understanding of the immunopathogenesis of prolonged community-acquired pneumonia (CAP). The aim of the study was to study the cytokine profile of bronchoalveolar secretion in the prolonged course of CAP.

MATERIALS AND METHODS OF RESEARCH

In our research we studied 79 patients aged 25-56 years, undergoing treatment in the clinic for CAP. During the investigation patients were divided into two groups depending on the duration of the CAP. 38 patients (22 men and 16 women) were selected for group I, among which CAP of clinical group III was stated in 24 (63.2%) patients, VI – in 14 patients (36.8%) with a prolonged course of the disease. The group II included 41 patients (24 men and 17 women), with CAP of clinical group III verified in 29 (70.7%) patients, VI – in 12 patients (29.3%), who recovered within two-three weeks of treatment. Groups of patients were coherent in age and sex. Verification of the diagnosis of CAP was carried out according to the standardized protocols of diagnostics and treatment of respiratory diseases operating in Ukraine [1]. All patients gave informed consent to the processing of their data, as well as to the laboratory and instrumental methods used in the study.

The research was conducted in accordance with the principles of bioethics set out in the WMA Declaration

of Helsinki – "Ethical principles for medical research involving human subjects" and "Universal Declaration on Bioethics and Human Rights" (UNESCO).

In patients of groups I and II, on the first and last 1-2 days of hospital stay, in the obtained from the affected area of the lungs during fibrobronchoscopy perfomed according to the standard method BAS there was determined concentration of pro-inflammatory (IL-1β, IL-2, TNFα, IL-6, IL-8) and anti-inflammatory CK (IL-4 and IL-10) [9]. The ratio of the CK opposition pools, particularly IL-1β/IL-10 and TNFα/IL-10, was calculated. To determine the cytokine profile of BAS, the test systems certified in Ukraine manufactured by the NGO Protein Contour (ProCon) were used. The study of the concentration of CK was performed by solid-phase ELISA using laboratory equipment manufactured by Sanofi Diagnostics Pasteur (France), including enzyme-linked immunosorbent assay PR 2100 [3], according to the instructions of the manufacturer. The study results were compared with the CK concentration in BAS, obtained by examining 25 healthy individuals, identical in age and sex. Conventional therapy and symptomatic treatment were used to treat patients with CAP diagnosis [1].

The standard application packages, such as Microsoft Microsoft 7, Microsoft Office 2007 (product number 89409-707-4157945-65726 2007) were used for the statistical processing of the obtained research results. The basic principles of using statistical research methods in clinical trials were used as well [2].

RESULTS AND DISCUSSION

While studying the CK BAS, it was found that the acute period of CAP in patients of both groups revealed probable changes in the concentration of both pro-inflammatory and anti-inflammatory CK (Table 1). Thus, in group I, the level in IL-1β was higher than expected by 8.4 times ($p<0.01$), in group II – by 5.9 times ($p<0.01$). Comparative analysis of biological fluid in the studied samples, the concentration of this CK in patients of both groups showed that in the patients of group I, on admission to the hospital, the level of IL-1β was by 1.4 times ($p<0.05$) higher than in patients of group II. The level of other pro-inflammatory CK IL-2 in group I, compared with the norm, increased by 9.1 times ($p<0.01$) in group II – by 4.8 times ($p<0.01$). In the intergroup comparison, the concentration of IL-2 in patients of group I, on average, was by 1.9 times ($p<0.05$), higher than the value of a similar indicator in patients of group II. On admission to the hospital, all patients had a probable increase in the concentration of TNF-α in BAS. In patients of group I, the concentration of TNF-α in BAS increased on average by 9.5 times ($p<0.01$), in group II – by 6.3 times ($p<0.01$). A comparative analysis of the level of TNF-α in the comparison groups showed that in patients of group I, the level of TNF-α in BAS on average was by 1.5 times ($p<0.05$) higher than in group II.

When studying the level of other pools of pro-inflammatory CK, particularly IL-6 and IL-8, an increase in their concentration in BAS in patients of both groups was also found. Thus, in patients of group I, the level of IL-6 in BAS was higher than usual on average by 11.8 times ($p<0.01$), the concentration of IL-8 increased by 7.4 times ($p<0.01$), in group II the content of these CK was higher than average by 6.7 ($p<0.01$) and 4.2 times ($p<0.01$) respectively. Besides, it was found that the multiplicity of increase in the level of IL-6 and IL-8 in BAS in patients with prolonged course of CAP was by 1.8 times ($p<0.05$) higher than in patients who recovered within two to three weeks of treatment.

Thus, studying the cytokine profile of BAS in the acute stage of CAP, it was found that in patients of both groups, in the biological substrate studied, there was an increase in the level of the pool of pro-inflammatory CK. Significantly, these changes were more pronounced in group I, i.e. in patients who subsequently had a prolonged course of CAP.

Analysis of the level of the pool of anti-inflammatory CK in BAS in the acute period of CAP showed considerable increases in their concentration in the bronchoalveolar space. In particular, in patients of group I, the level of IL-4 in BAC was higher than usual, on average by 3.7 times ($p<0.01$), the concentration of IL-10 increased by 3.2 times ($p<0.01$), in group II the content of these CK was higher than average by 6.7 ($p<0.01$) and 4.6 times, ($p<0.01$) respectively. At the same time, in the intergroup comparison, the concentration of IL-4 in BAS in patients of group I, was lower by 1.8 times ($p<0.05$), than the value of this indicator in patients of group II, and the level of IL-10 was lower by 1.4 times ($p<0.05$) respectively.

According to the changes in the BAS in the acute period of the CAP the level of pro-inflammatory and anti-inflammatory CK and changes in coefficients were noted, which characterize the ratio of their opposition pools. Thus, the increase in IL-1β/IL-10 compared with the reference rate in group I was by 2.8 times ($p<0.05$), in group II – by 1.4 times ($p<0.05$). Comparative analysis of IL-1β/IL-10 in both study groups showed that the value of this coefficient in group I was by 2.0 times ($p<0.05$) higher than in group II. Compared with the norm, the value of TNF-α/IL-10 in the subjects of groups I and II increased by 3.4 times ($p<0.01$) and 1.6 times ($p<0.05$) respectively. In the intergroup comparison, the value of the studied coefficient in patients of group I was by 2.1 times ($p<0.01$) higher than the value of TNF-α / IL-10 in group II.

Table 1

Level of CK in BAS in the examined patients in the acute period of CAP Me (Q25; Q75)

Analyzed indicator	Norm	Groups of patients		p**
		I (n=38)	II (n=41)	
IL-1β (pg/ml)	3.28 (3.18; 3.54)	27.6 (25.67; 29.31) p*<0.01	19.3 (17.78; 20.64) p*<0.01	<0.05
IL-2 (pg/ml)	1.6 (1.52; 1.71)	14.5 (13.63; 15.37) p*<0.01	7.6 (7.14; 8.06) p*<0.01	<0.05
TNF-α (pg/ml)	21.8 (20.12; 23.76)	208.1 (189.4; 224.6) p*<0.01	138.4 (130.08; 148.05) p*<0.01	<0.05
IL-6 (pg/ml)	2.1 (1.97; 2.25)	24.8 (22.56; 26.53) p*<0.01	14.1 (13.12; 14.81) p*<0.01	<0.05
IL-8 (pg/ml)	17.8 (16.38; 19.22)	132.5 (124.55; 140.47) p*<0.01	74.3 (69.09; 78.02) p*<0.01	<0.05
IL-4 (pg/ml)	1.4 (1.31; 1.52)	5.11 (4.71; 5.42) p*<0.01	9.37 (8.81; 10.02) p*<0.01	<0.05
IL-10 (pg/ml)	1.91 (1.74; 2.07)	6.18 (5.79; 6.61) p*<0.001	8.71 (8.10; 9.23) p*<0.001	<0.05
IL-1β/IL-10	1.62 (1.4; 1.9)	4.47 (4.01; 4.89) p*<0.05	2.22 (1.95; 2.43) p*<0.05	<0.05
TNF-α/IL-10	9.86 (8.9; 10.74)	33.67 (29.28; 37.04) p*<0.01	15.89 (13.81; 17.42) p*<0.05	<0.05

Notes: * – reflects the probability of differences of each indicator relative to the norm according to the Mann-Whitney U-test; ** – the probability of the difference between the corresponding indicators in patients of groups I and II according to the Mann-Whitney U-test.

Thus, the above changes in the ratio of pro-inflammatory and anti-inflammatory CK indicate a significant predominance of the pro-inflammatory activity of BAS in this period of the survey. Also, in the acute period of CAP in patients who subsequently had a prolonged course of the disease, a more significant predominance of the pro-inflammatory activity of BAS was noted.

When re-determining the level of CK, i.e. after completing conventional therapy in groups I and II, the dynamics of improvement of the disturbed indicators was different. Thus, in group I, compared with the original study, the concentration of IL-1β in BAS decreased by 2.0 times ($p<0.05$), in group II – by 2.9 times ($p<0.05$), the content of IL-2 – by 2.4 times ($p<0.05$) and 2.5 times ($p<0.05$) respectively. Although complete recovery of IL-1β and IL-2 concentrations in BAS in both groups at discharge from the hospital did not occur, in patients of group I the content of IL-1β and IL-2 was by 2.04 times ($p<0.05$) and 1.95 times ($p<0.05$) higher than in the group II (Table 2).

When studying the level of TNF-α there was found a decrease in its concentration in BAS compared with the acute period of CAP, in group I – by 2.23 times ($p<0.05$), in group II – by 3.41 times ($p<0.05$). Although complete recovery of this indicator in both study groups at discharge from the hospital did not occur, in patients of group I the content of TNF-α was by 2.3 times ($p<0.05$) higher than its concentration in BAS in group II.

The content of other pro-inflammatory CK IL-6 in patients of group I compared with the original study decreased by 2.41 times ($p<0.05$), IL-8 – by 1.78 times ($p<0.05$), in group II – by 2.71 times ($p<0.05$) and 2.05 times ($p<0.05$). Complete recovery of IL-6 and IL-8 concentration in BAS in both groups at discharge from the hospital did not occur. However, in patients of group I, the content of IL-6 was by 1.98 times ($p<0.05$), IL-8 – by 2.06 times ($p<0.05$) higher than in the group II. Therefore, when studying the cytokine profile of BAS after CAP treatment, it was found that patients in group I had more pronounced pro-inflammatory activity of BAS.

Table 2

Level of BAS in CK in the examined patients after conventional treatment of CAP Me (Q25; Q75)

Analyzed indicator	Norm	Groups of patients		p_2
		I (n=38)	II (n=41)	
IL-1β (pg/ml)	3.28 (3.18; 3.54)	13.4±2.6 (12.58; 14.34) p*<0.05	6.57±1.42 (6.21; 6.96) p*<0.05	<0.05
IL-2 (pg/ml)	1.6 (1.52; 1.71)	5.96±1.03 (5.65; 6.38) p*<0.05	3.05±0.54 (2.86; 3.26) p*<0.05	<0.05
TNF-α (pg/ml)	21.8 (20.12; 23.76)	93.2±16.1 (86.67; 99.72) p*<0.05	40.6±7.9 (38.16; 43.04) p*<0.05	<0.05
IL-6 (pg/ml)	2.1 (1.97; 2.25)	10.3±2.1 (94.81; 11.21) p*<0.05	5.2±1.3 (4.87; 5.61) p*<0.05	<0.05
IL-8 (pg/ml)	17.8 (16.38; 19.22)	74.5±15.1 (69.28; 80.46) p*<0.05	36.2±5.8 (34.04; 38.73) p*<0.05	<0.05
IL-4 (pg/ml)	1.4 (1.31; 1.52)	3.18±0.41 (2.89; 3.41) p*<0.05	1.95±0.14 (1.79; 2.06) p*<0.05	<0.05
IL-10 (pg/ml)	1.91 (1.74; 2.07)	5.12±0.48 (4.71; 5.48) p*<0.05	2.91±0.25 (5.269; 3.08) p*<0.05	<0.05
IL-1β/IL-10	1.62 (1.4; 1.9)	2.62±0.46 (2.35; 2.83) p*<0.05	2.26±0.54 (2.07; 2.46) p*>0.05	>0.05
TNF-α/IL-10	9.86 (8.9; 10.74)	18.2±2.9 (16.19; 19.65) p*<0.05	13.95±2.1 (12.83; 15.21) p*>0.05	>0.05

Notes: * – reflects the probability of differences of each indicator relative to the norm according to the Mann-Whitney U-test; ** – the probability of the difference between the corresponding indicators in patients of groups I and II according to the Mann-Whitney U-test.

Complete recovery of anti-inflammatory CK in both groups after completion of conventional treatment did not occur. Nevertheless, less pronounced positive changes in the concentration of these CK also occurred in patients of group I. In particular, the concentration of IL-4 in group I in this study period exceeded the reference rate by 2.3 times ($p<0.01$). In group II, after completion of conventional treatment, the content of IL-4 was by 4.8 times ($p<0.01$) lower than in the original study and by 1.4 times ($p<0.05$) higher than reference value. Comparative analysis of this CK level in patients of both groups showed that in group I the concentration of IL-4 in BAS was by 1.6 times ($p<0.05$) higher than in group II.

Changes in the level of other pro-inflammatory CK IL-10 after treatment in both groups had a similar direction. Complete recovery of CK in both groups on discharge from the hospital also did not happen: the concentration of IL-10 in group I exceeded the reference rate by 2.7 times ($p<0.01$), in group II – in by 1.5 times ($p<0.05$). In the intergroup comparison, the concentration of IL-10 in BAS in patients of group I was by 1.8 times ($p<0.05$) higher than the level of CK in group II. Therefore, when studying the cytokine profile of BAS after the end of CAP treatment, we found that patients of group I, along with more significant pro-inflammatory activity of BAS, more pronounced pro-inflammatory activity of BAP was preserved.

Complete recovery of IL-1β/IL-10 and TNF-α/IL-10 coefficients in group I patients before discharge from the hospital did not occur. The values of IL-1β/IL-10 and TNF-α /IL-10 in group I exceeded the reference ones by 1.7 and 1.8 times, respectively ($p<0.05$). In contrast to patients of group I, in group II during this study period the values of IL-1β/IL-10 and TNF-α/IL-10 decreased and probably did not differ from the reference norm ($p>0.05$).

Thus, in the early stages of CAP, there was an increase in the level of pro-inflammatory and anti-inflammatory CK in BAS and a significant disorder of the ratio of their opposition pools towards

increasing pro-inflammatory activity. Patients with a prolonged course of CAP had more significant disorders of the cytokine profile of BAS, which was expressed in a considerable increase in the level of pro-inflammatory (IL-1β, IL-2, TNF-α, IL-6 and IL-8) and anti-inflammatory CK (IL-4 and IL-10) as well as an increase in pro-inflammatory activity, as evidenced by an increase in IL-1β/IL-10, TNF-α/IL-10. During the standard therapy of CAP, in patients with a prolonged course of the disease, the cytokine profile of BAS was not fully restored.

CONCLUSIONS

1. In patients with a prolonged course of CAP in its acute period, changes in the BAS system were more significant than in patients with non-prolonged course.
2. In the intergroup comparison, in the case of a prolonged course of CAP, BAS recorded an increase in the concentration of pro-inflammatory CK (IL-1β 1.4 times, IL-6 and IL-8 – by 1.8 times, TNF-α – by 1.5 times, IL-2 – by 1.9 times), a decrease in anti-inflammatory (IL-4 – by 1.8 times, IL-10 – by 1.4 times) and a more significant disproportion in the ratio of their opposition pools, as evidenced by an increase in IL-1β/IL-10 – by 2.0 times, TNF-α/IL-10 – by 2.1 times.
3. In the conditions of the standard therapy in patients with prolonged and non-prolonged course of CAP, various rates of improvement of CK in BAS indicators are defined. In patients with prolonged CAP, the rate of improvement of pro-inflammatory and anti-inflammatory CK was slower. At the time of discharge from the hospital, most patients had an imbalance of pro-inflammatory and anti-inflammatory CK with a predominance of pro-inflammatory activity in the bronchoalveolar space.
4. Based on the obtained data, in the future, it can be considered appropriate to determine the pathogenetic role of CK and imbalances in their system during prolonged CAP to conduct a study of the content of CK in the serum.

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