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Influence of complex therapy on the concentrations of C-reactive protein and interleukin-2 in patients with pulmonary sarcoidosis

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Abstract

The research work is related to the development of new prognostic criteria in the course of sarcoidosis that are based on the analysis of changes in the indices of C-reactive protein and IL-2 in bronchoalveolar lavage. The study of violation patterns of these indices at the molecular level of intercellular interaction by means of modern laboratory-instrumental diagnostic methods will certainly allow to quickly, easily and accurately identify the process activity, make reasoned prognosis and find appropriate preventive treatment policy for every patient individually.

Keywords: Sarcoidosis, activity markers, prognosis

1. Introduction

The prevalence of respiratory disorders has become one of the topical issues in modern medicine, as they subsequently lead to the excess incidence, disability and mortality.

Among various respiratory pathologies interstitial diseases keep attracting attention of scientists due to continuous disease incidence (interstitial processes account for about 20% of all pulmonary diseases), problems with diagnosis and management. Progressive fibrosis of pulmonary interstitium causes respiratory failure and pulmonary hypertension with the development of chronic cor pulmonale and untenable disability [2, 6].

Interstitial lung diseases (ILD) constitute a heterogenous group of diseases, often of unknown etiology, which are characterized by progressive lung injury with inflammatory-sclerotic changes in the structure of pulmonary interstitium. According to WHO's estimates, in the XXI century the number of potential years of life lost due to ILD will be comparable to those lost due to lung cancer [9].

Currently, sarcoidosis is one of the most common interstitial lung diseases of unknown origin. For example, this pathology accounts for 27% of all ILD cases in Belgium, 34.1% in Greece and 33.7 in Italy [7, 10]

Sarcoidosis is an inflammatory granulomatous disease of unknown etiology, in which 90-95% of cases are characterized by lung damage. It is necessary to identify the criteria of disease activity in order to evaluate the course of the inflammatory process. In spite of the development of radiological diagnostic methods, identification of highly accurate laboratory criteria is currently important, as they will make it possible to prognosticate the course of disease and evaluate the effectiveness of treatment.

To manage the patient with sarcoidosis a doctor must not only make the diagnosis and determine the extent of the process, but also identify its activity and predict further course of the pathology.

Usually, sarcoidosis may run the following courses: spontaneous regression, regression on treatment, stabilization, progression, undulating course and recurrence.

A doctor must have substantial reasons to administer active treatment, thus he must make sure that the absence of treatment may have considerable negative consequences for the patient.

The following criteria are most often used to evaluate the activity of inflammatory process [1, 6, 12, 14]:

1. Lofgren's, Heerfordt-Waldenstrom's Syndromes.
2. Onset (worsening) of complaints – cough, dyspnea.
3. Signs of extrapulmonary manifestations of the disease.
4. Increased ACE levels by 1.5 times and more.
5. Leukocytosis, ESR, hypercalcemia.

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6. Increased CD4/CD8 ratio in BAL fluid.
7. Deterioration of respiratory function.
8. Progression of radiographic manifestations.

Currently, there are no dominant activity markers that may clearly estimate the level of disease progression, need for systemic therapy and monitoring of the effectiveness of administered treatment.

C-reactive protein (CRP) is an early nonspecific, yet sensitive marker of tissue inflammation and damage, and is determined in various acute pulmonary and extrapulmonary infections [13]. C-reactive protein is an acute-phase protein that instantly responds to inflammation and appears in blood plasma within 4-6 hours after tissue as a result of various factors. Due to the fact that concentration changes of C-reactive protein are directly associated with the severity and dynamics of clinical manifestations, it is widely used as the most sensitive clinical-and-laboratory indicator of inflammation while monitoring and controlling the effectiveness of treatment of various diseases [11, 14]. The increase of C-reactive protein in bronchoalveolar lavage occurs under the influence of proinflammatory cytokines, particularly IL-6 and IL-2, as well as its penetration from blood as a result of failure in blood-air barrier arising from constantly persisting inflammation.

Early diagnostics of recurrent attacks is considerably important because of high relapse rates of the disease. Process activity identification is of great practical value as it enables the clinician to formulate personal prognosis for every patient, choose adequate therapeutic approach and evaluate the effectiveness of administered treatment.

2. Materials and methods of investigation.

68 patients with pulmonary sarcoidosis underwent profound instrumental examination before treatment and after three-month management; the average age of patients was (35.7±6.6) years. All of them underwent inpatient treatment at the pulmonology department of regional center of phthisiology and pulmonology (Ivano-Frankivsk).

Verification of the diagnosis of sarcoidosis and its formulation was made according to the materials of the order of the Ministry of Health care of Ukraine №634 from September 08, 2014 "On approval and implementation of medical and technological documents on medical care standardization in sarcoidosis".

The control group comprised 16 apparently healthy individuals (AHI).

All patients underwent the complex of general clinical examination techniques suitable for patients with sarcoidosis (physical examination, X-ray study, multispiral computed tomography, spirometry, fiber-optic bronchoscopy, clinical and laboratory diagnostics). The levels of C-reactive protein and IL-2 in bronchoalveolar lavage were also determined.

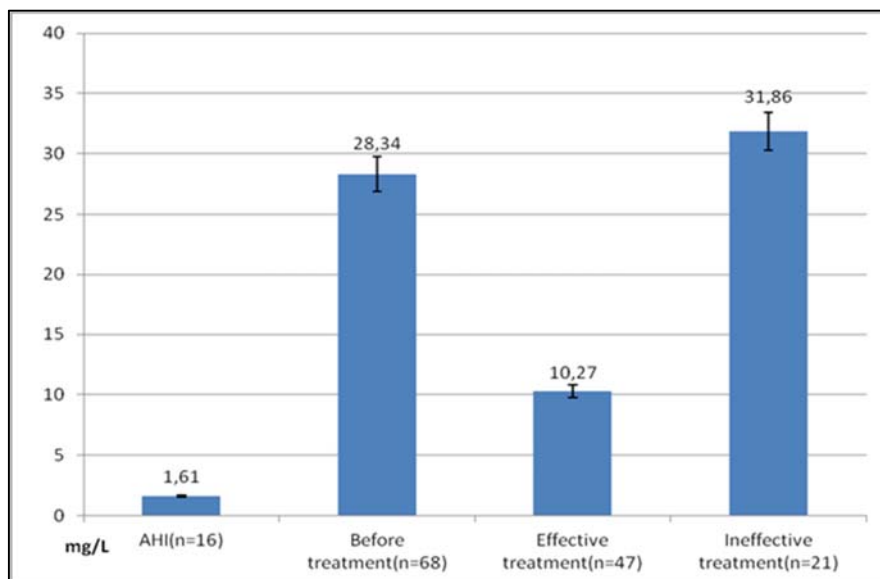
The level of IL-2 was studied by enzyme immunoassay on the "StatFax 303 Plus" analyzer with the help of "Interleukin-EIA" reagents in bronchoalveolar lavage obtained during fiber-optic bronchoscopy by Clements S. procedure in Ramirez H. modification, taking into account the location of lung damage in patients with sarcoidosis before and after three-month treatment. The level of C-reactive protein was determined by semi-quantitative latex particle agglutination test with the help of «Dialab» reagent kit (Austria). Statistical processing of the studied material was performed using licensed Microsoft Excel analysis package.

Multispiral computed tomography of thoracic organs was performed using Toshiba Aquilion Prime scanner, with subsequent recording of findings on digital medium and assessing the density of lung tissue by Hounsfield unit (HU) scale: when the density of lung tissue in dynamics was less than 893.5 Hounsfield units the treatment was considered effective, but if the density of lung tissue, as compared to initial indices, exceeded 893.5 units the treatment was considered ineffective.

All patients were treated according to unified protocol: peroral glucocorticosteroids in a dosage of 0.5 mg/kg of body weight per prednisolone dose for four weeks. Thereupon the dose was reduced within eight weeks so that to the end of the third month it made up 0.25 mg/kg. Additionally, patients were administered potassium asparaginate - 0.158 g/magnesium asparaginate - 0.14 g as one tablet twice a day, vitamin E 400 mg once a day, and, if necessary, treatment of comorbid conditions according to standards. The effectiveness of treatment was assessed three months after its start according to standard criteria (complaints, objective findings, multispiral computed tomography of thoracic organs, chest X-ray, ESR, spirometry, concentration of angiotensin-converting enzyme).

3. Results and discussion

The analysis of the findings showed that the concentration of C-reactive protein in patients with active pulmonary sarcoidosis (n=68) before treatment was (28.34±2.45) mg/L ($p<0.05$), that is 17.6 times higher as compared to control group (n=16) – (1.61±0.17) mg/L ($p<0.05$).

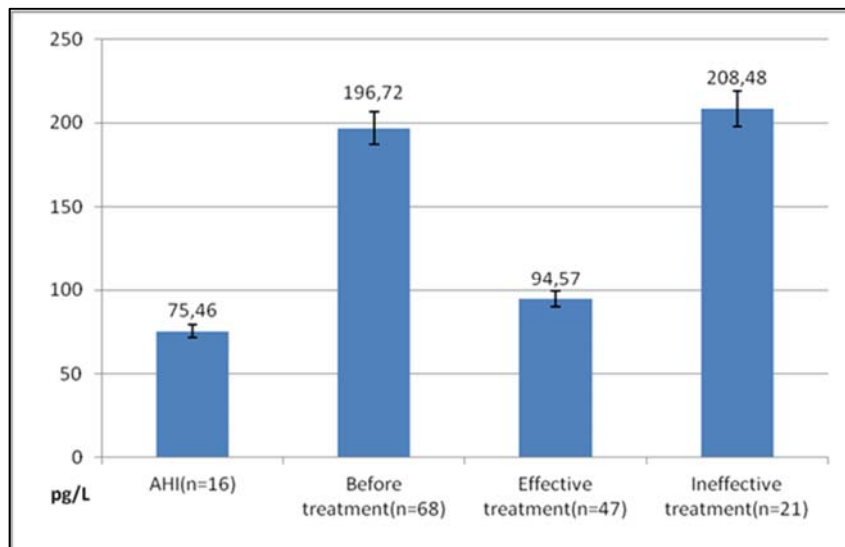


Picture 1: CRP concentration in patients with pulmonary sarcoidosis before and after three-month treatment.

The re-evaluation of this index after three-month treatment showed that the CRP level was considerably lower (10.27 ± 1.18 mg/L ($p < 0.05$)) in patients ($n = 47$) with diagnosed effectiveness of treatment, while the concentrations of CRP remained increased (31.86 ± 2.64 mg/L ($p < 0.05$)) in patients ($n = 21$) whose treatment failed.

As was showed in table 1, the level of Interleukin-2 correlated to CRP level, and was 2.61 times increased in active pulmonary sarcoidosis as compared to the control one

(75.46 ± 5.26 pg/L) ($p < 0.05$) and made up (196.72 ± 8.13) pg/L ($p < 0.05$). After three-month treatment the examination revealed that the concentration of IL-2 in BAL of patients with positive clinicoradiologic dynamics was 2.08 times lower and made up (94.57 ± 4.23) pg/L ($p < 0.05$). This marker tended to increase in patients with verified inadequacy of assigned treatment and made up (208.48 ± 10.12) pg/L ($p < 0.05$).



Picture 1: IL-2 concentration in patients with pulmonary sarcoidosis before and after three-month treatment.

These findings correlated to the results of general clinical examination and dynamics of changes on multispiral computed tomography of thoracic organs.

4. Conclusions

1. The level of C-reactive protein in bronchoalveolar lavage in active pulmonary sarcoidosis increases by 17.6 times as compared to apparently healthy individuals (AHI) ($p < 0.05$) and makes up (28.34 ± 2.45) mg/L.
2. The level of interleukin-2 in bronchoalveolar lavage in

active pulmonary sarcoidosis increases by 2.61 times as compared to control group ($p < 0.05$) and makes up (196.72 ± 8.13) pg/L.

3. After three-month treatment the concentration of C-reactive protein in bronchoalveolar lavage decreased to (10.27 ± 1.18) mg/L, that is 2.76 times lower as compared to initial indices ($p < 0.05$) and indicates the effectiveness of treatment and conforms the indices of dynamics on multispiral computed tomography of thoracic organs.
4. The level of interleukin-2 decreased by 2.08 times, and

made up (94.57±4.23) pg/L as compared to initial concentrations ($p<0.05$) that suggests the effectiveness of treatment and relates to the results of multispiral computed tomography of thoracic organs.

5. Retained high concentrations of C-reactive protein (31.86±2.64) mg/L and interleukin-2 (208.48±10.12) pg/L after three-month treatment indicate inadequacy of the administered therapy.

Table 1: Levels of C-reactive protein and interleukin-2 in bronchoalveolar lavage of patients with pulmonary sarcoidosis

Indices	AHL, n=16	Pulmonary sarcoidosis		
		Before treatment, n=68	After treatment	
			Effective treatment, n=47	Ineffective treatment, n=21
CRP, mg/L	1.61±0.17	28.34±2.45	10.27±1.18	31.86±2.64
IL-2, pg/L	75.46±5.26	196.72±8.13	94.57±4.23	208.48±10.12

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