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Clinical case: treatment of severe bronchial asthma patients with neutrophilic inflammation type

Key words: *severe asthma, neutrophilic type of inflammation, clinical case.*

To the problem of asthma has long paid much attention each year, improving approach for diagnosis and maintenance of advanced disease, developing and implementing new drugs regimen. However, to achieve controlled asthma in patients is not possible.

Severe asthma is characterized with uncontrolled course, low pulmonary function, severe clinical symptoms, frequent exacerbations and ambulances, limitation of lifestyle and quality of life on standard therapy, resulting in significant social and economic costs [7, 9].

The dominant pathophysiological feature of asthma is airway inflammation, sometimes accompanied by structural changes in the airways, which leads to remodeling [8, 15, 19]. Underlying inflammation in the bronchi in severe asthma is increased activity of eosinophils, mast cells, macrophages, Th2 lymphocytes, epithelial cells, with subsequent release and activation of cytokines and various inflammatory mediators that contribute to chronic disease [14, 28].

Pathophysiology of severe asthma is characterized by varying degrees of bronchial hyperresponsiveness (BH) [27]. In severe asthma often we can see consistently low FEV_1, decreased BH, like in COPD. It is possible to conclude that in severe asthma, as well as in chronic obstructive pulmonary disease, there is an irreversible or partially reversible component of bronchial obstruction [12, 30].

Asthma is a heterogeneous disease with many phenotypes. Identification of specific phenotypes of asthma pathophysiology improves our understanding of the disease predicts and response to therapy, lead to a better selection of both existing and future treatment of asthma in each case [10, 11].

The use of non-invasive markers of airway inflammation suggest the presence of three different phenotypes of asthma: neutrophilic, eosinophilic, and mixed low- granulocyte types of inflammation [3, 22]. Recent studies suggest that these groups may differ in their etiology, immunopathology and response to treatment [14, 21].

Ordonez C. L. and colleagues showned in several studies that in sputum in patients with severe asthma are dominated neutrophils and IL-8 [24].

Recently, there was information about the possibility of using statins in respiratory diseases such as COPD [20]. Doctors are well known for their hypolipidemic effect, but brought other pleiotropic properties of statins: anti-inflammatory, immunomodulating, antioxidant, improve the function of the epithelium, and others. [1, 2, 17, 18, 25, 26, 31].

These multicenter randomized clinical trials indicate decreased activity of all inflammatory markers under the influence of statins [13, 28]. Anti-inflammatory effect provided by such mechanisms as improving of endothelial function by increasing the levels of NO, shortness of thrombosis (due to decrease platelet aggregation and lower fibrinogen (which increases during remodeling resulting from severe asthma), tissue plasminogen activator inhibitor type 1) [19, 23, 30]. Statins positively influence on the migration of macrophages and functional status, as well as the migration and proliferation of smooth muscle cells in the vessel wall, thus

improving its biochemical and histochemical characteristics. In particular, by inactivation of macrophages, they reduce the production of proinflammatory cytokines and metalloproteases such as IL8. It is proved that lovastatin inhibits the production of IL- 8 in human alveolar epithelium, which potentially leads to a positive effect of statins in the treatment of neutrophil inflammation in the airways [22, 25, 26].

Experimental studies show a decrease of inflammatory markers such as C -reactive protein plasma and inflammatory cells of atherosclerotic plaques under the influence of statins [17]. These effects may be related to inhibition of steroid compounds of izoprenoide [5].

Designated anti-inflammatory effects of certain statins led us to suggest that some statins (atorvastatine) may exhibit an auxiliary anti-inflammatory effect in patients with severe asthma insufficiently controlled with standard anti-inflammatory therapy, and can be an effective addition to the recommended basic treatment of severe asthma and improve control of disease.

We perform our own clinical case observations (work carried out by the state budget).

Patient K., 70 years was on outpatient treatment in the department of diagnostic, therapy medicine and clinical pharmacology of lung diseases because of the severe persistent asthma. He admitted with complaints of constant daytime symptoms of asthma, frequent exacerbations, frequent nocturnal symptoms, limitation of physical activity, coughing, shortness of breathing. Daily fluctuations of peak volume integral expiratory flow rate (SEU type) during peakflowmethry was> 20%. The patient noted stroke cough with mucous expectoration to 20 ml per day, with a slight shortness of breath on exertion, weakness. Sick for 40 years. Aggravation 2-3 times a year. Proper control of asthma symptoms and functional impairmentwas not reached on basic therapy with inhaled corticosteroids (fluticasone propionate) – 1000 mg per day in combination with β_2-agonist long-acting (salmeterol), which was used at a dose of 100 mg daily, and salbutamol as needed.

An objective examination: during auscultation – impaired breathing bilaterally with single dry rales, bilateraly. Cardial tons sonorous, rhythmic cardiac contraction. In X-ray examination marked fibrous roots, emphysematous lungs. The study of respiratory function (PFT) found vent in violation of obstructive type (FEV_1 – 67,3 %). After pharmacological tests with bronchodilators FEV_1 reversibility was 13 %. Prior to treatment the average asthma-score was 5.0, the average number of inhalations of salbutamol per day was – 0.7.

Induced sputum was analyzed. local immunity indices are presented in Table 1.

A calculation of the results obtained by the formulas:

$I_{Gr} = N_{Eph} / N_{Nph} = 24 / 44 = 0.5.$

$I_M = (N_{AMph} + N_{Lph}) / (N_{Eph} + N_{Nph}) = (25 + 7) / (24 + 44) = 0.5.$

Studies of changes in the local immunity of the patient revealed in K. neutrophilic type of inflammation.

The patient continued with fluticasone propionate at a dose of 250 mcg and salmeterol at a dose of 25 mg – 2 inhalations 2 times a day for 1 month.

Against the background of basic therapy the patient slightly decreased cough, sputum allocated in small amounts, shortness of breathing durine moderate exertion, disturbed nocturnal symptoms, daytime asthma symptom not decline. Average asthma score was 4.8 points; the average number of inhalations of salbutamol per day was 0.8. (FEV_1 increased to 71.9 %). After pharmacological tests with bronchodilators reversibility FEV1 was 2.6 %.

Study of local and systemic immunity before to treatment revealed significant increase in the number of neutrophils in induced sputum to 73 %, increased levels of proinflammatory cytokines – IL6 to 18.5 pg / ml and 700 pg IL8 / ml (see tab. 2).

In system also were noted negative changes – decrease of percentage of phagocytic cells to 17 % and NBT test to 17.6 um. units. (see tab. 3). After basic therapy cellular redistribution of cells remained at the same level. The content of neutrophils in induced sputum was 70 % of the total cell population. Decreased levels of pro-inflammatory cytokines – IL6 to 12.1 pg / ml and IL8 610 pg / ml were observed. Slightly increased the percentage of phagocytic cells, their phagocytic number and oxygen -dependent metabolism.

Table 1

Survey results of local bronchi immunity (induced sputum) patient K

	Indicies	Results	Normal	Dinamic
1	Content eosinophils (%)	24,0	to 2,0 %	(+)
2	Content neutrophils (%)	44,0	to 8,0 %	(+)
3	Content lymphocytes (%)	7,0	11,0 – 14,0	(–)
4	Content macrophages (%)	25,0	82,0 – 90,0	(–)

Table 2

Indices of local and systemic immunity in step basic treatment

Indices	NEUTR %	EOS %	LYM %	PAM %	IL6 (pg /ml)	IL8 (pg /ml)
Before treatment	73	3	7	17	18,5	700
Base therapy	70	5	13	12	12,1	610

Patient K., 70 years continued outpatient treatment returned for a second consultation in 4 weeks. After the therapy with fluticasone propionate at a dose of 250 mcg and salmeterol at a dose of 25 mg – 2 inhalations 2 times a day, and salbutamol as needed condition his state, improved, but has not been received proper control of asthma symptoms and functional impairment was not achieved, patient complains of intermittent cough with mucous expectoration to 20 ml per day, dyspnea on exertion, fatigue.

Objective: bilaterally tapped single dry rales on expiration during auscultation. Cadial tons sonorous, rhythmic cardiac contraction. The study of respiratory function (PFT) found vent in violation of obstructive type (FEV_1 – 71,9 %). After pharmacological tests with bronchodilators reversibility FEV_1 was 2.6 %. Prior to treatment the average asthma-score was 4.8 points, the average number of inhalations of salbutamol per day was – 0.8.

Against the background of basic therapy the patient was prescribed treatment with atorvastatin 10 mg per day during 1 month.

1 month after the combined therapy with atorvastatin significantly reduced cough, decreased sputum production, shortness of breathing appeared with moderate exertion, nocturnal symptoms disappeared, severity of daytime asthma symptoms decreased significantly. Average asthma score became 2.1, the average number of inhalations of salbutamol per day decreased to 0.2. Indicators FEV_1 increased to 76.7 %. After pharmacological tests with bronchodilators reversibility FEV_1 became 8.9 %.

Against the background of basic therapy status of local immunity was altered for neutrophils in induced sputum, levels of proinflammatory cytokines were significantly higher than normal. State of systemic immunity was suppressed (see Table. 4).

The inclusion of atorvastatin to basic therapy significantly improved indices of system and local immunity. Fully normalized cellular composition of induced sputum significantly decreased levels of interleukin IL 8 to 70 pg / ml, but the level of IL 6 increased slightly to 29.2 pg / ml, possibly due to the activation of macrophages.

Significantly increased the percentage of phagocytosis to 56% and phagocytic number Nph 12.5 um. Units, and oxygen-dependent metabolism of granulocytes to 93.3 um. units. (see tab. 5).

Hence, the inclusion of atorvastatin to the basic treatment of the patient K., who has identified the type of neutrophilic inflammation, lead to fewer asthma attacks, shortness of breathing, morning chest tightness, the need for rescue medication, decrease of bronchial obstruction (FEV_1 increased from 67.3 to 76.7 %), normalization of phagocytic cells, disappearance or significant reduction of signs of inflammation, normalization of cellular composition of induced sputum and improvement in functional status granulocytes local protection.

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Table 3

Indices of systemic immunity in step basic treatment

Indices	Percentage of phagocytosis (%)	phagocytic number (conventional units)	Granulocites NST. (conventional units)	CRP (mg/ml)
Before treatment	17	6,18	17,6	5
Base therapy	29	7,07	18,8	5

Table 4

Dinamics of indices of local and systemic immunity after basic treatment with addition of atorvastatin

Indices	NEUTR %	EOS %	LYM %	PAM %	IL6 (pg /ml)	IL8 (pg /ml)
Before treatment	73	3	7	17	18,5	700
Base therapy	70	5	13	12	12,1	610
Base therapy+atorvastatine	7	0	7	82	29,2	70

Table 5

Dynamics of indices of systemic immunity in after basic treatment with addition of atorvastatin

Indices	Percentage of phagocytosis (%)	phagocytic number (conventional units)	Granulocites NST. (conventional units)	CRP (mg/ml)
Before treatment	17	6,18	17,6	5
Base therapy	29	7,07	18,8	5
Base therapy+atorvastatine	56	12,5	93,3	5

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КЛИНИЧЕСКИЙ СЛУЧАЙ: ЛЕЧЕНИЕ БОЛЬНОГО С ТЯЖЕЛОЙ БРОНХИАЛЬНОЙ АСТМОЙ С НЕЙТРОФИЛЬНЫМ ТИПОМ ВОСПАЛЕНИЯ

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Резюме. *Тяжелая бронхиальная астма (БА) остается актуальной проблемой современной медицины. В последнее время в научной литературе отражение гетерогенности воспаления при БА привело к выделению разных форм, фенотипов и эндотипов заболевания. Поэтому новым направлением в диагностике БА является определение маркеров заболевания и индивидуализированный подход к лечению. В статье изложены особенности диагностики, клинических симптомов и лечения тяжелой БА с нейтрофильным типом воспаления на примере собственного наблюдения автора.*

Ключевые слова: *тяжелая бронхиальная астма, нейтрофильный тип, клинический случай.*

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CLINICAL CASE: TREATMENT OF PATIENTS WITH SEVERE ASTHMA WITH NEUTROPHIL TYPE INFLAMMATION

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Summary. *Severe asthma remains an actual problem in modern medicine. In recent scientific literature reflected heterogeneity of inflammation in asthma that led to the isolation of different modes, phenotypes and endotypes of disease. Therefore, a new direction in the diagnosis of this disease is to identify markers of disease and individualized approach to treatment. The article contains diagnostic features, clinical symptoms and treatment of severe asthma with neutrophil type of the inflammation on the example of the of author's observations.*

Keywords: *severe asthma, neutrophil type, clinical case.*

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