ORIGINAL ARTICLE

CONTENTS

Asthma in patients with the syndrome of undifferentiated dysplasia of connective tissue: peculiarities of the course or mutually aggravating mechanisms?

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ABSTRACT

Aim: To analyse laboratory and biochemical features of the severe persistent course of asthma in patients with undifferentiated connective tissue dysplasia (UCTD) syndrome, and their phenotypic and visceral stigmas of dysembryogenesis.

Materials and Methods: We enrolled 60 male patients with asthma, aged from 23 to 62 years (mean age (46.83 ± 0.85) years): 30 patients with the background of UCTD, and 30 - without UCTD. We analysed clinical, somatometric, surveying (original questionnaire based on the phenotypic map of Glesby), instrumental (spirography, echocardiography, endoscopy, esophagofibrogastroduodenoscopy) and laboratory (including eosinophilic granulocytes and aldosterone levels) data.

Results: Correlations were found in men with UCTD between the number of UCTD markers and rate of earlobe diagonal fold ($r=+0.75$; $p<0.05$), asthenic constitution ($r=+0.72$; $p<0.05$), easy bruising ($r=+0.7$; $p<0.05$) and straight abdominal line hernia ($r=+0.52$; $p<0.05$). Average aldosterone serum level in patients with UCTD (176,10 ± 11,22) was significantly higher than in those without UCTD (142,77 ± 9,43), ($p<0.05$), as well as average eosinophils levels (1.3 ± 0.25 vs. 0.57 ± 0.12, $p<0.05$). In the absolute majority of patients with UCTD (93.3%) asthma onset was confirmed after pneumonia, and their age of asthma manifestation was significantly higher (37.2 ± 1.21) than in patients without UCTD (21.4 ± 1.13). Also, in patients with UCTD there was a high number of severe exacerbations during the last year (2.7 ± 0.12 per year) on the background of high doses of combined inhaled glucocorticosteroids use.

Conclusions: Identified "phenotypic profile", clinical and biochemical features of patients with asthma on the background of UCTD syndrome, which determine the severe course and early formation of asthma complications, will further accelerate the diagnosis of this asthma phenotype and improve approaches to the selection of treatment regimens for these patients.

KEY WORDS: asthma, undifferentiated connective tissue dysplasia, eosinophils, aldosterone

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INTRODUCTION

Asthma is one of the most important medical and social problems. The disease affects all age categories of the population and, with ineffective control, leads to a significant impairment of the quality of life, and in some cases, to the death of patients. Today, the heterogeneous nature of asthma is described in many scientific publications [1-4], its diversity is reflected in the GINA guidelines in the new definition of the disease [5], and the concept of asthma phenotype is increasingly being introduced into clinical practice, which should be taken into account when choosing a treatment regimen [6, 7].

The doctor's daily practice shows that clinical response to the proposed therapy of patients with the same disease severity may be different.

Polyvalent sensitization is recognized as one of the prerequisites for the severe course and development of fatal asthma complications [8, 9]. Today, molecular and statistical methods are used to determine clinical phenotypes. Continuous research, that would allow finding a connection between the phenotype, genotype, mechanism of disease development and the body's response to disease therapy, is being conducted, and thus improving the choice of drugs, taking into account the specifics of the course of asthma [9-11].

In pulmonology practice, asthma is defined as the result of complex interaction of environmental factors and genetic predisposition [12-14]. Pathomorphological changes in this disease are characterized by the accumulation of inflammatory effector cells in the submucosal layer of the bronchial tree, hyperplasia of mucous glands, accumulation of deposits in the submucosal matrix, degranulation of mast cells, hypertrophy and hyperplasia of bronchial smooth muscle and thick-

ening of the subepithelial collagen layer [4, 9, 15-17]. The involvement of collagen in the pathomorphological changes in asthma can become an interesting common pathogenetic link in the general picture of the course of this disease in people with undifferentiated connective tissue dysplasia syndrome (UCTD) - a hereditary connective tissue (CT) disorder of the same heterogeneous nature as asthma and a fairly high prevalence in the population [8, 9, 18,19-21].

AIM

The aim of our study was to analyse laboratory and biochemical features of the severe persistent course of asthma in patients with UCTD syndrome, and their phenotypic and visceral stigmas of dysembryogenesis.

MATERIALS AND METHODS

Clinical characteristics of the examined patients. For the period from 2018 to 2023, 103 male patients with a verified diagnosis of asthma, who were undergoing inpatient treatment in the National Pirogov Memorial Medical University clinic therapeutic department, were examined.

To achieve the goal, among them we selected 60 patients with a diagnosis of: "asthma, non-allergic, severe persistent course, uncontrolled", aged from 23 to 62 years (mean age (46.83 ± 0.85) years).

The diagnosis of asthma was established in accordance with medical care protocol for patients with bronchial asthma [22], WHO classification, and taking into account the recommendations of the Global Initiative for Asthma - GINA, 2022 [5].

Patients were divided into two groups. The main group (group I) included 30 men with asthma on the background of UCTD, aged from 36 to 62 years, average age (50.11 ± 1.28) years. The comparison group (group II) consisted of 30 men with asthma without UCTD (number of phenotypic and visceral stigmas of UCTD 5 or less), aged from 23 to 54 years, average age (43.53 ± 1.29) years.

Analysis of anamnestic data of both groups of patients revealed certain features, in particular: the onset of the disease in patients of group I was significantly later: (37.2 ± 1.21) years, against (21.4 ± 1.13) years in group II. The first episode of asthma in the absolute majority of patients with UCTD (93.3%) was established after pneumonia. No such anamnestic feature was found in group II.

In addition, among patients with asthma on the background of UCTD, there is a significantly higher number of severe exacerbations during the last year against the background of the use of high doses of combined inhaled glucocorticosteroids (GCS) - (2.7 ± 0.12 per year) versus (1.9 ± 0.1) in patients without UCTD ($p<0.05$).

Exclusion criteria were concomitant nosologies associated with hypereosinophilia: systemic diseases of CT, helminthiasis, skin diseases, allergic diseases, malignant neoplasms, pulmonary eosinophilia.

Clinical and instrumental studies were performed on all patients, followed by statistical processing of the data obtained. In particular, the following was carried out:

Somatometric examination (analysis of the following anthropometric features by the method of Bunak modified by Shaparenko [23] such as body weight, body length, torso length, neck length, chest length, lower limbs length, head circumference, chest circumference) [24].

Survey of patients. All subjects were surveyed using a specially designed original questionnaire based on the phenotypic map of Glesby in the modification of Martinov and co-authors [23]. The questionnaire included 54 positions of microanomalies. Based on examination, the number of UCTD stigmas was counted. The diagnosis of UCTD was established by detecting 6 or more positions of microanomalies [24].

Instrumental methods. Determination of the external breathing function (EBF) was carried out on a BTL 08 SpiroPRO computer spirograph (Great Britain). The reversibility of bronchial obstruction was studied in the inhalation test with a short-acting β2-agonist (salbutamol at a dose of 400 μg).

Structural and hemodynamic characteristics of the heart muscle were determined using echocardiography. Echocardiography and Doppler cardiography were performed in standard positions on a General Electric Vivid 7 Dimension ultrasound system (USA). Visceral stigmas were determined using the data of ultrasound examination of the internal organs of the abdominal cavity using the General Electric "Logic- 7" (Vivid – 3) (USA).

Laboratory methods. All patients underwent general clinical and biochemical tests in the accredited clinical and biochemical laboratory of Synevo Ukraine LLC (accreditation cert. No. 30016, valid until March 15, 2025). In particular, a general blood test was performed with the calculation of the absolute level of eosinophils (in g/l) and serum aldosterone (pg/ml). Prior to the study, alcohol intake, smoking, food intake, physical activity was limited, and medications intake was excluded.

The normative absolute value of the eosinophilic granulocytes level in the blood is 0.12-0.5 g/l. Eosinophilia is defined as this level is greater than 0,5 g/l. Hypereosinophilia is defined as moderate to severe eosinophilia (≥1,5 g/l). Monitoring of the eosinophils

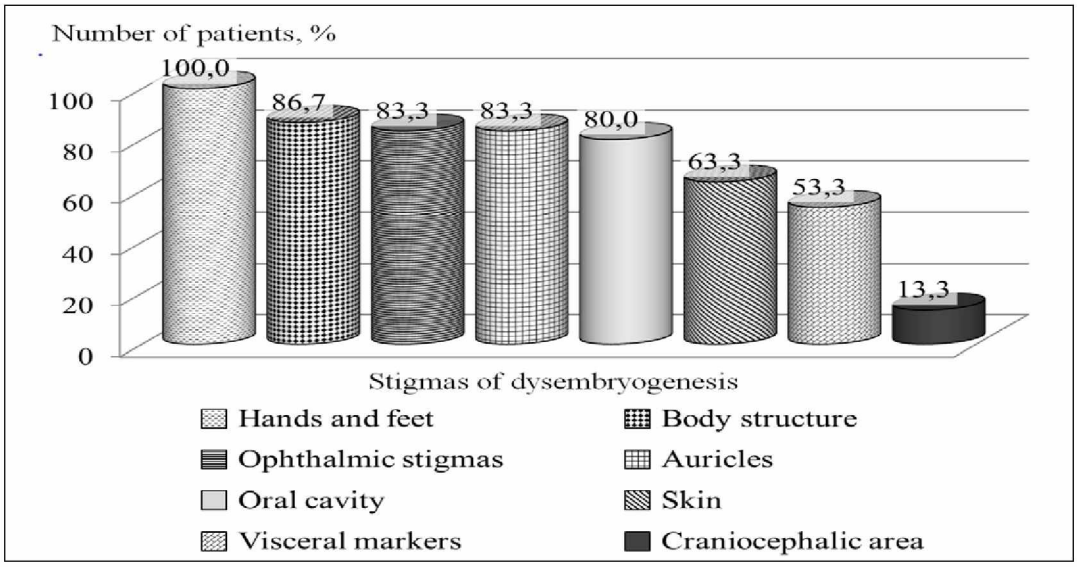

Fig. 1. Qualitative analysis of stigmas of dysembryogenesis in patients with asthma and UCTD.

level was carried out regularly (at least once a week), during each exacerbation of asthma during the year of observation.

Determination of the aldosterone level was carried out by the method of solid-phase enzyme-linked immunosorbent assay (ELISA) using the DRG analyser and test system (Germany). The design of our study provided that in patients with uncontrolled asthma, the level of aldosterone was determined no earlier than six months after the last exacerbation of the disease or hospitalization with the use of systemic GCS. Normative indicators of aldosterone in serum: in the supine position - (10.0 - 160.0) pg/ml.

Data analysis was performed in SPSS Statistics v.23. Summary statistics of mean, standard deviation and percentiles were used for quantitative measurements. The association between measures was assessed using the correlation test and t-test. The probability value was estimated at 0.05 confidence level (P=0.05).

RESULTS

The analysis of UCTD markers in both groups revealed that the average number of stigmas in patients of group I was 10.41 ± 0.35, and in patients of the group II - 4.48 ± 0.16. The majority (73.3%) of people of group I (with UCTD) showed a high level of stigmatization (13 or more stigmas).

Qualitative analysis of stigmas of dysembryogenesis by lesion location in group I revealed the features shown on Fig. 1. In particular, among patients' phenotypic stigmas, we most often noted: lateral clinodactyly – in 93,3% patients, 4th finger is longer than 2nd – in 73,3%, asthenic constitution – in 80%, scoliosis – in 56.7%, radial-lacunar iris and diagonal fold of the earlobe – in 60%, diastema – in 43,3% of patients. Frequency of visceral stigmas were somewhat inferior: easy bruising – in 30%, varicose veins of the lower extremities – in 26,7%, hernia of the abdomen straight line – in 16,7% of patients.

Direct strong correlations were found in men with UCTD between the number of UCTD markers and the frequency of detection of the diagonal fold of the earlobe (r=+0.75; p<0.05), asthenic constitution (r=+0.72; p< 0.05), easy bruising (r=+0.7; p<0.05); direct correlations of medium strength - for the radial-lacunar type of the iris (r=+0.64; p<0.05) and hernia of the straight abdominal line (r=+0.52; p<0.05).

The data we obtained are to some extent consistent with the data of other authors and our own studies conducted on another cohort of patients [24, 25].

The study of the levels of eosinophils and aldosterone in patients revealed the following features (Table 1).

The average level of aldosterone in serum of patients in group I was above the norm, and in group II it did not go beyond the normative indicators. In addition, a statistically significant difference (p<0.05) was established in the average aldosterone levels between patients with asthma on the background of UCTD and those with asthma without UCTD.

Therefore, almost a quarter of patients in group I (23.3%) had a significantly elevated aldosterone level, compared to only 6.7% of patients in group II.

Analysis of average values of blood plasma eosinophils levels in patients with asthma confirmed that number of eosinophils in patients of group I was much higher than normal level, and significantly higher than in patients of group II. (1.3 ± 0.25 vs. 0.57 ± 0.12, p<0.05). Eosinophilia is a typical laboratory finding, typical for

Table 1. Distribution of eosinophils and aldosterone levels in patients with asthma (n=60)

Indicators	Patients with UCTD (n=30)		Patients without UCTD (n=30)	
	Levels	Number of patients, %	Levels	Number of patients, %
Total average level of eosinophils, g/l	1,3 ± 0,25*	100	0,57 ± 0,12	100
Normal level of eosinophils, g/l	0,42 ± 0,10	20	0,43 ± 0,11	33,3
High level of eosinophils, g/l	1,42 ± 0,28	80	0,81 ± 0,19	66,7
Total average aldosterone level, pg/ml	176,10 ± 11,22*	100	142,77 ± 9,43	100
Total average level of eosinophils, g/l	1,3 ± 0,25*	100	0,57 ± 0,12	100
Normal aldosterone level, pg/ml	145,74 ± 16,41	76,7	132,85 ± 11,16	93,3
High aldosterone level, pg/ml	280,56 ± 24,04	23,3	178,34 ± 26,89	6,7

$p<0.05$, * - the difference is significant between the main and the comparison group.

most patients with severe asthma [9, 18]. In a large part of our patients, we found eosinophilia in both groups of the study. However, in such patients with asthma on the background of UCTD, the average number of eosinophils reached a higher level (1.42 ± 0.28).

It should be noted that just among patients with a large number of stigmas (12 or more) and increased aldosterone level and hypereosinophilia (≥1.5 g/l), the largest number of patients (5 men) had combination of dysembryogenesis stigmas as following: asthenic constitution, hernia of the abdomen straight line and easy bruising.

DISCUSSION

The obtained data suggest the search for the role of elevated aldosterone level and moderate eosinophilia in the pathogenesis of asthma in UCTD.

The accumulation of inflammatory effector cells in the submucosal layer of the bronchial tree plays a significant role in the formation of the components of bronchial obstruction in asthma. Besides, eosinophilic inflammation is dominant in asthma. Eosinophilia as a phenomenon is the result of myelopoiesis on the one hand, and the destruction and fixation of eosinophils in the tissues on the other. What exactly affects the increase in eosinophils in the blood of patients with asthma against the background of UCTD syndrome? Attention is drawn to the fact that in the anamnesis of patients with asthma on the background of UCTD, there is a high number of severe exacerbations during the last year (2.7 ± 0.12 per year) on the background of the use of high doses of combined inhaled GCS and the late onset of asthma at a fairly mature age. The combination of an elevated level of eosinophils in the blood and this clinical symptomatology is typical for severe eosinophilic asthma, where the leading pathogenetic link of immune damage is an increase in the level of interleukin-5 (IL-5). Hyperproduction of IL-5 is accompanied by absolute eosinophilia, since this cytokine specifically regulates the maturation of eosinophils, enhancing the differentiation of progenitor cells and the proliferation of eosinophils in the bone marrow, activates the interaction between eosinophils and endotheliocytes, which leads to increased adhesion and migration of eosinophils, strengthening of chemokine connections with eosinophils, activation and destruction of mature eosinophils [14, 17, 18].

Another interesting biochemical feature of the group of patients with asthma on the background of UCTD is the increased level of aldosterone. It is known that the synthesis and secretion of cortisol and aldosterone are regulated according to the law of feedback by the hypothalamic-pituitary-corticosuprarenal apparatus [13, 24, 25]. The level of eosinophils in peripheral blood depends on the level of adrenocorticotropic hormone and adrenal cortex hormones [9]. Therefore, a decrease in adrenocorticoid activity accelerates the release of eosinophils from the bone marrow. In patients with asthma on the background of UCTD, this mechanism also has the right to exist and can determine both the features and the severity of the course of the disease.

Eosinophil is primarily a tissue cell. The end point of eosinophil migration is the skin and mucous membranes of organs that have direct contact with the environment, in particular, the lungs. Migration of eosinophils to tissues is controlled by chemotactic factors, including complement components, histamine, leukotrienes, lymphokines, tumor-associated factors, and IL-5 [18]. At the same time, activated by the chronic inflammatory process, these factors together with eosinophils stimulate the accumulation of fibrin in the lumen of the alveoli and small bronchi, which ultimately leads to an increase in collagen formation in the lungs. If this process is accompanied by inefficient resorption of CT, as well as excessive regeneration and repair, the normal architecture of the lung tissue is distorted and eventually pneumofibrosis develops.

Fibrosis is traditionally viewed as a progressive pathological process that involves numerous cellular and molecular mechanisms that lead to the accumulation of excess carbohydrate-protein matrix components in the extracellular space. Sweating of fibrinogen in the composition of various plasma proteins in the lumen of the respiratory tract is one of the manifestations of inflammation of the respiratory tract. It is known that fibrin, which is formed from fibrinogen, inactivates the surfactant in the alveoli, thereby contributing to the collapse of the alveoli and the deepening of diffusion-perfusion disorders [17].

Hypersecretion of transforming growth factor beta and type I collagen DNA should be highlighted among the known mechanisms of aldosterone's fibrotic action. Aldosterone induces local inflammatory processes in the endothelium of medium and small vessels, increases the level of plasminogen activator inhibitor. It is a proven fact that with a long-term (more than 3 weeks) persistent increase of aldosterone, there is a significant acceleration of the proliferation of fibroblasts with excessive accumulation of collagen I and III ("wrong") types and with a pronounced stimulation of the processes of perivascular fibrosis, the formation of interstitial fibrosis and the so-called "expansion" of interstitial tissue. The morphological substrate of this action of aldosterone is the presence of receptors on endothelial cells and fibroblasts [24, 25]. Back in 1997, W. Timens and co-authors put forward a hypothesis about the role of fibroblast dysfunction in the development of emphysema. Fibroblasts synthesize components of the extracellular matrix: collagen, elastin, proteoglycans, and also interact with immune and inflammatory cells with the help of cytokines. The first and third types of collagen perform the function of interstitial tissue stabilizer. Failure of fibroblasts to ensure adequate tissue homeostasis can lead to abnormal repair with the formation of emphysema. It is obvious that the development of pulmonary fibrosis occurs not so much as a result of enhanced collagen synthesis, but as a result of a violation of its metabolism. Also, when the level of aldosterone increases, the physiological regulation of mineralocorticoid receptors in macrophages with the initiation of pro-inflammatory cytokines that support the process of chronic inflammation is disturbed [25].

The multifunctional nature of CT determines its distribution in all organs and systems of the human body [24]. The significant content of abnormal collagen types I and III in patients with UCTD, in particular, in the lung tissue, suggests that atypical protein-polysaccharide complexes fixed in such defective CT, and other antigens of local and tissue origin may serve as a target for immunopathological processes [7, 11].

Such mutually aggravating mechanisms of increased levels of eosinophils and aldosterone, which are observed in patients with asthma on the background of UCTD, lead to the maintenance of a chronic inflammatory process in the lungs and accelerated fibrosis in the lungs. Chronic inflammation in the bronchopulmonary system stimulates the processes of increasing collagen formation in the lungs, mediated by various factors, which can further lead to the development of fibrous changes in the bronchi walls and pneumofibrosis with the formation of emphysema and respiratory failure [5].

CONCLUSIONS

1. Features of the course of asthma in patients with UCTD syndrome include late onset of asthma, debut after pneumonia, severe course of the disease (frequent exacerbations on the background of using high doses of inhaled GCS), elevated levels of eosinophils and aldosterone in serum, presence of such phenotypic stigmas: asthenic constitution, hernia of the abdomen straight line and easy bruising.
2. The revealed increased levels of eosinophils and aldosterone in serum in patients with asthma on the background of UCTD are mutually aggravating in terms of maintaining the processes of chronic inflammation and accelerated fibrosis in the lungs, which can be prognostically unfavorable in the formation of early pneumofibrosis, emphysema of the lungs, and respiratory failure.

The identified "phenotypic profile", clinical and biochemical features of patients with asthma on the background of UCTD syndrome, which determine the severe course and early formation of asthma complications, will further accelerate the diagnosis of this phenotype of asthma and improve approaches to the selection of treatment regimens for such patients.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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