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CORRELATIONS BETWEEN CLINICAL SEVERITY OF PULMONARY TUBERCULOSIS, THYROID FUNCTION AND SOME CYTOKINES

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Резюме: Корреляции между клиническим течением туберкулеза легких, функцией щитовидной железы и некоторыми цитокинами.

С целью оценки взаимовлияния тиреоидного профиля, некоторых цитокинов и клинической тяжести течения деструктивных форм впервые диагностированного туберкулеза легких обследовано 43 больных впервые диагностированным туберкулезом легких и 10 здоровых лиц. Всем больным до начала лечения и лицам из группы контроля проведено ультразвуковое исследование эхоструктуры щитовидной железы, а также определены уровни содержания свободного тироксина, тиреотропного гормона гипофиза, антител к тиреоглобулину и тиреопероксидазе в системном кровотоке параллельно с определением уровне содержания фактора некроза опухолей-альфа, интерферона-гамма, интерлейкинов-2, -6, -4. Изучались корреляции между клиническим течением впервые диагностированного туберкулеза легких, функцией щитовидной железы и данными цитокинами. Более чем у половины больных туберкулезом выявлены изменения эхоструктуры щитовидной железы. У всех больных установлено снижение уровня содержания свободного тироксина до низко-нормальных значений этого показателя. При туберкулезе, сочетавшемся с телепатиями, отмечено более значительное снижение уровня тироксина и повышение уровня тиреотропного гормона гипофиза. Продемонстрировано повышение уровней содержания провоспалительных цитокинов: фактора некроза опухолей-альфа и интерлейкина-6. и снижение уровня противовоспалительного интерлейкина-4 у больных туберкулезом в сравнении со здоровыми. Установлена положительная корреляция между уровнями тироксина, интрлейкина-6 и клинической тяжестью туберкулеза. Большой процент выявленных тиреопатий обосновывают необходимость скрининга функционального состояния щитовидной железы у больных туберкулезом для выявления его скрытых нарушений и их коррекции с целью восстановления цитокинового равновесия и улучшения исходов туберкулезного процесса.

Ключевые слова: туберкулез легких, щитовидная железа, иммунитет, цитокины.

Summary.

To estimate the interrelations between thyroid profile, some cytokines and clinical severity of new case of cavitary pulmonary tuberculosis 43 patients with cavitary pulmonary tuberculosis and 10 healthy volunteers were studied. Thyroid glands of all patients before chemotherapy and volunteers from control group were examined by ultrasound. The levels of free thyroxine, thyroid stimulating hormone and antibodies to thyroglobulin and thyroid peroxidase in the serum were defined. At the same time the levels of tumor necrosis tumor necrosis factor, interferon-gamma and interleukin-2, -6, and -4 were measured. Correlations between clinical severity of new case of pulmonary tuberculosis, thyroid functions, and these cytokines were studied. The pathological changes of thyroid echo structures were recovered in more than half of patients. The level of thyroxine in tuberculous patients was decreased down to lower-normal significance. In tuberculous patients with pathological echo structure of the thyroid the thyroxine level decreasing was more significant. The thyroxine stimulating hormone level was increased in these patients. The increasing of tumor necrosis tumor factor and the interleukin-6 levels and the decreasing of interleukin-4 level were demonstrated in tuberculous patients comparing with healthy persons. Positive correlation between clinical severity of new case of pulmonary tuberculosis, thyroid functions, and these cytokines were determined. The high percentage defined cases of thyroid pathology in tuberculous patients is caused the necessity the screening of thyroid function in tuberculous patients for in time diagnosis of its subclinical disorders and their correction to restore cytokines balance and improving of antituberculosis chemotherapy efficacy.

Key words: pulmonary tuberculosis, thyroid, immunity, cytokines.

Rezumat: Corelația dintre severitatea clinică a tuberculozei pulmonare, funcția tiroidiană și unele citokine

Pentru a estima interrelațiile dintre profilul tiroidian, unele citokine și severitatea clinică a unui nou caz de tuberculoză pulmonară cavitară au fost studiate 43 de pacienți cu tuberculoză pulmonară cavitară și 10 voluntari sănătoși. Glanda

tiroidă ale tuturor pacienților înainte de chimioterapie și voluntarii din grupul de control au fost examinată prin examen ultrasonor. Au fost definite nivelurile de tiroxină liberă, hormon de stimulare a tiroidei și anticorpi la tiroglobulină și peroxidază tiroidiană în ser. În același timp, au fost măsurate nivelurile de factor de necroză tumorală, interferon-gamma și interleukina-2, -6 și -4. Au fost studiate corelațiile dintre severitatea clinică a tuberculozei pulmonare caz nou, funcțiile tiroidiene și aceste citokine. Modificările patologice ale structurilor eco tiroidian au fost recuperate la mai mult de jumătate dintre pacienți. Nivelul de tiroxină la pacienții cu tuberculoză a fost scăzut până la o semnificație normală mai scăzută. La pacienții cu tuberculoză cu structură eco patologică a tiroidei, scăderea nivelului de tiroxină a fost mai semnificativă. Nivelul hormonului de stimulare a tiroxinei a fost crescut la acesti pacienti. Creșterea factorului tumoral de necroză tumorală și a nivelurilor de interleukină-6 și scăderea nivelului de interleukină-4 au fost demonstrate la pacienții cu tuberculoză comparativ cu persoanele sănătoase. S-a determinat corelația pozitivă între severitatea clinică a noului caz de tuberculoză pulmonară, funcțiile tiroidiene și aceste citokine. Procentul mare de cazuri definite de patologie tiroidiană la pacienții cu tuberculoză a determinat necesitatea screening-ului funcției tiroidiene la pacienții cu tuberculoză pentru diagnosticarea la timp a tulburărilor sale subclinice și corectarea acestora pentru restabilirea echilibrului citokinelor și îmbunătățirea eficacității chimioterapiei antituberculoase.

Cuvinte cheie: tuberculoză pulmonară, tiroida, imunitate, citokine.

Introduction.

According to modern concepts, tuberculosis refers to interleukin-dependent immunodeficiency, accompanied by pronounced changes in the cytokine network of the human body. Cells of the monocyte-macrophage system are activated by the thyroid gland (TG) in direct and indirect ways, which contributes to the elimination of the causative agent of tuberculosis from the body [2,10]. The aim of the study is to study the mutual influence of thyroid homeostasis, cytokine profile and clinical severity of the disease in patients with destructive forms of firstly diagnosed pulmonary tuberculosis (FDTB).

Materials and methods.

Inclusion criteria: common destructive forms of firstly diagnosed pulmonary tuberculosis (FDTB).

Exclusion criteria: Age of patients under 18 years of age, pregnancy.

The study included 43 patients with firstly diagnosed pulmonary tuberculosis treated in the hospital of the Kharkov regional tuberculosis dispensary No.1. Among them, men - 28; 15 women aged from 18 to 60 years (mean age 34.12 years) and 20 healthy volunteer donors with unchanged thyroid echostructure, who made up the control group.

Before treatment, all patients underwent an ultrasound examination of the echostructure of the thyroid gland, in the systemic circulation the levels of free thyroxine (free T4), pituitary thyroid stimulating hormone (TSH), antibodies to thyroglobulin (TG) and thyroperoxidase (TPO) were examined in parallel with the determination of cytokines levels, most actively involved in the formation of anti-inflammatory response to tuberculosis infection: tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interleukins: IL-2; IL-6; IL-4. The echostructure of the thyroid gland was visualized using the diagnostic ultrasound machine SSF-240A manufactured by Toshiba Medical Systems.

Free thyroxine and thyroid-stimulating hormone, antibodies to thyroglobulin and thyroperoxidase as well as levels of cytokines in the blood serum were determined by enzyme immunoassay using kits on a Tecan Sunrise spectrophotometer (Austria).

The study of the main clinical indicators, the prevalence and nature of radiological changes in the lungs, as well as the massiveness of bacterial excretion was carried out using a scoring (Table 1,2). The following criteria were taken into account: the severity of intoxication and bronchopulmonary syndrome, the prevalence and nature of radiological changes in the lungs, as well as the massiveness of bacterial excretion. The point assessment of intoxication was carried out on the basis of two quantitative parameters: body temperature, measured in degrees Celsius and body weight deficiency in kilograms (Table 1).

Table 1.

Ball score of the prevalence of pulmonary involvement and tuberculosis intoxication

Quantity of balls	Volume of lung involvement	Number of cavitations in the lungs	Body temperature	Underweight	Total maximum points
1	1 lobe of lung	1	Under 38.0ºC	Under 10kg	
2	2 lobe of lung	2-3	Under 39.0ºC	Under 20kg	
3	More than 2 lobes	4 and more	Over 39.0ºC	Over 20kg	
Maximum points	3	3	3	3	12

When assessing the bronchopulmonary syndrome, the presence and severity of cough, sputum, hemoptysis, and shortness of breath were taken into account (Table 2).

seous pneumonia - 3; disseminated tuberculosis -1; fibrous-cavitary tuberculosis -2. Destructions in the lungs were present in 40 patients (92.92%). Bacterial excretion was found in 41 patients (97.56%).

Table 2.

Ball score of bronchopulmonary syndrome

Quantity of points	Cough	Sputum	Hemoptysis	Dyspnea	Total maximum points
1	Mild (minor cough in the morning)	Under 10 ml/day	Present	When walking fast or going uphill	
2	Moderate. (cough. in the morning and during the day)	Under 30 ml/day	Present	When walking at a normal pace on level ground	
3	Strong	Over 30 ml/day	Present	At rest	
Maximum balls	3	3	3	3	12

Table 3.

Indicators of the thyroid profile in patients with FDTB depending on the echostructure of the thyroid gland

Parameter	Group 1 (healthy persons) (n=10)	Group 1 (FDTB) (n=21)	Group 1 (FDTB+thyroid pathology) (n=22)	Confidence factor
T_4 free (pmol/l)	14.76 ± 0,23	12.24 ± 0,13	10.02 ± 0,16	$P_{1,2} < 0,05$ $P_{1,3} < 0,05$ $P_{2,3} < 0,05$
TSH(mcIU/l	1.39 ± 0,57	1.37 ± 0,18	2.72 ± 1,31	$P_{1,2} > 0,05$ $P_{1,3} < 0,05$ $P_{2,3} < 0,05$
A/b to TG	7.60 ± 3,82	25.38 ± 4,91	39.32 ± 12,68	$P_{1,2} < 0,05$ $P_{1,3} < 0,05$ $P_{2,3} > 0,05$
A/b to TPO	4.68 ± 1,27	3.24 ± 0,39	19.71 ± 16,07	$P_{1,2} < 0,05$ $P_{1,3} < 0,05$ $P_{2,3} > 0,05$

Massiveness of bacterial excretion was assessed according to generally accepted criteria (absence of M T B- 0 points; MTB 1+ - 1 point; MTB 2+ - 2 points; MTB 3+ - 3 points; MTB 4+ - 4 points). Thus, with a total assessment of the severity of clinical, radiological and laboratory parameters, the maximum possible number of points is 26.

Statistical processing of the obtained data was carried out by the method of variation statistics using a standardized Microsoft Excel XP calculation package. The probability of discrepancy between the mean values was determined by Student's t-test. The correlation between the linear parameters was determined by the Pearson index. The critical level of significance (P) when testing statistical hypotheses was taken equal to 0.05.

Results.

According to clinical forms, patients were distributed as follows: Infiltrative tuberculosis -37 cases; ca-

Ultrasound examination of the echostructure of the thyroid gland revealed the presence of thyroid pathology in 22 patients (51.16%). Of these, 9 patients had grade 1th thyroid hyperplasia; in 5 - hyperplasia of the gland of 1-2 degrees with signs of autoimmune thyroiditis in the form of granularity of its structure and mosaic echogenicity; in 6 - gland hypoplasia of the 1st degree. In 7 patients, signs of autoimmune thyroiditis were found without changes in the volume of the gland. The detected changes in the echostructure of the thyroid gland in more than half of the examined patients with tuberculosis indicate a high risk of dysfunction of this organ in tuberculosis. Even the initial stages of enlargement of the thyroid gland of 1-2 degrees with euthyroidism are identified with thyroid dysfunction, which, in turn, negatively affects various organs and systems [6,18,10].

In accordance with the results of preliminary screening of thyroid pathology using ultrasound, the

patients were divided into two groups: group 1 (patients with normal echostructure of the thyroid gland) and group 2 (patients with pathological echostructure of the thyroid gland).

In the study of the hormonal profile in most tuberculosis patients with normal thyroid structure (group 1), low-normal values of free T4 (12.24 ± 0.13 pmol/ml) were revealed. In tuberculosis patients with thyroid gland pathology (group 2), this indicator dropped to the borderline value and amounted to 10.02 ± 0.16 pmol/ml. When comparing the average values of free thyroxine, a significant decrease in its level was found in the group of patients with thyroid pathology (Table 3).

The level of thyroid-stimulating hormone in the systemic circulation in the group of patients with normal echostructure of the thyroid gland was within the physiological norm of 1.37 ± 0.16 mcIU/ml. The level of TSH in the group of patients with pathology of the echostructure of the thyroid gland significantly increased compared with group 1 (Table 3) and amounted to 2.72 ± 1.31 mIU/ml. It should be noted that at present in modern endocrinology there is a discussion about the standards of thyroid-stimulating hormone. Moreover, the main discussions are related to the upper limit of the normal TSH [2]. Recent recommendations from the US National Academy of Clinical Biochemistry suggest narrowing the normal range for TSH levels from 0.4 to 2.5 mcIU/L [10].

The basis for this was the results of the NHANES-111 study, which showed that when examining 13,344 individuals, no more than 5% of the iodine-provided area had a TSH level exceeding 2.5 mcIU/l [9]. In the European SHIP study, TSH levels were also 2.12 mcIU/mL in 95% of 1488 individuals examined [32]. According to the Wickham study, in the group of individuals with a TSH level above 2 mcIU / ml [2,30,31], overt hypothyroidism is more often diagnosed. Thus, a "normally" high TSH level reflects the earliest in terms of onset and mildest thyroid insufficiency [28]. Taking into account these data, the level of TSH in group 3 can be considered a marker of minimal thyroid pathology for tuberculosis patients with altered echostructure of the thyroid gland.

The levels of antibodies to thyroglobulin, as well as to thyroperoxidase, did not exceed the normal allowable values in both groups of patients with FDTB, however, both indicators with U/ml increased significantly in the group of patients with FDTB with thyroid pathology compared with the group of healthy individuals. The content of antibodies to TG was 25.38 ± 4.91 U/ml in the group of patients with FDTB with normal echostructure of the thyroid gland. This indicator significantly increased to 39.32 ± 16.68 U/ml in the group of patients with pathological changes in the echostructure of the thyroid gland. The concentration of antibodies to TPO was 3.24 ± 0.39 U/ml in patients with unchanged gland structure and significantly increased to 19.71 ± 16.07 U/ml in patients with pathological gland structure.

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In a comparative analysis of the data obtained, it was found that in patients with FDTB with a pathology of the echostructure of the thyroid gland, compared with patients with FDTB with an unchanged structure of the gland, there were lower values of free thyroxin, an increased level of thyroid-stimulating hormone, as well as an increase in the level of antibodies, both to thyroglobulin and thyroperoxidase. The data obtained indicate a change in the thyroid profile in patients with pathological echostructure of the thyroid gland. Minimal thyroid dysfunction in this group of patients

Table 4.

Point assessment of the severity of the clinical course of FDTB depending on the thyroid pathology

Clinical criteria	Group 2 (n=21)	Group 2 (n=22)	p
Chest x-ray picture	2.09 ± 0.83	5.97 ± 0.76	<0.05
Bronchopulmonary syndrome	7.29 ± 1.53	7.59 ± 1.95	>0.05
Intoxicative syndrome	2.89 ± 0.95	5.58 ± 1.03	<0.05
Massive bacterial excretion	2.99 ± 0.34	3.27 ± 1.76	>0.05
Overall assessment of the severity of clinical manifestations	16.62 ± 3.36	22.27 ± 4.61	>0.05

is not an adaptive process, but is a pathological state of thyroid metabolism, which subsequently leads to a progressive decrease in the functional activity of the thyroid gland [1,6,10].

In a comparative assessment of the severity of clinical manifestations (Table 4), a more severe running of the tuberculosis was found in persons with pathological changes in the echostructure of the thyroid gland, mainly due to the greater severity of the intoxication syndrome and the prevalence of pulmonary lesions. In addition, in patients with severe destructive forms of newly diagnosed pulmonary tuberculosis, a negative correlation was established between the level of free thyroxine and the severity of the clinical course of tuberculosis (r = - 0.389). The study of the cytokine profile in the groups of patients with FDTB revealed a significant increase in the levels of TNF-α, INT-γ compared with the control, as well as a moderate increase in IL-2 and IL-6 and a decrease in the level of IL-4.

In a comparative study of the cytokine profile in groups 2 and 3 of patients with FDTB, in individuals with thyroid pathology, a lower level of values of all studied cytokines was found compared to individuals without thyroid pathology (Table 5).

pg/ml). ml). Considering the lower values of the T4 level in patients in the group of tuberculosis patients with thyroid pathology, as well as indications that thyroxine is a potential inducer of IFN-γ [12,13], it can be assumed that the production of IFN-γ is related to the level of thyroxine in the systemic circulation in patients with FDTB. The content of IL-2 in the systemic circulation in patients with FDTB of the lungs remained within acceptable physiological values (7.08 ± 1.97 pg / ml) with a decrease in this indicator by 2.5 times in patients with thyroid pathology (4.88 ± 1 05 pg/ml) compared with patients without thyroid disorders.

The levels of IL-4 in patients with VTD decreased compared with the control group. Lower values of this indicator were noted in persons with thyroid pathology and amounted to 0.002±0.003 pg/ml in group 2 and 0.030±0.027 pg/ml in group 3, respectively. The data obtained, apparently, are due to a significant increase in the level of IL-6, which is an antagonist of IL-4 that inhibits the secretion of IL-6 by macrophages. A decrease in IL-4 secretion enhances the body's resistance to tuberculosis infection and, thus, is a protective event in the formation of an immune response in patients with tuberculosis.

Table 5.

Levels of cytokines in peripheral blood in patients with FDTB without and with thyroid pathology

Study groups	TNF-α (pg/ml)	INT-γ (pg/ml)	IL- 2(pg/ml)	IL-6 (pg/ml)	IL-4(pg/ml)
Group1 (n=10)	0.53 ± 0.81	2.03±0.81	0.80±1,59	2.05 ± 0.59	0.001±0.001
Group2 (n=10)	60.84±25.01	3.74±2.45	7.08±1,97	51.87±33.54	0.002±0.003
Group3 (n=10)	30.77±16.77	1.22±0,81	4.88±1,05	16.98±11.81	0.030±0.027
$p_{1,2}$	<0.05	<0.05	<0.05	<0.05	<0.05
$p_{1,3}$	<0.05	<0.05	<0.05	<0.05	<0.05
$p_{2,3}$	<0.05	<0.05	<0.05	<0.05	<0.05

The level of TNF-α increased significantly in the FDTB groups by 120 times in patients without thyroid pathology and by 60 times in patients with thyroid pathology in comparison with healthy ones. An increase in the level of TNF-α is characteristic of patients with progressive tuberculosis and is an important factor providing specific cellular immunity, the formation of tuberculous granuloma, and blocking mycobacterial dissemination [3,27].

In patients with FDTB with impaired thyroid status, the level of TNF-α was 30.77±16.77 pg/ml, which is two times lower than the values of this indicator in patients with normal thyroid status (60.84±25.01 pg/ml).

The level of IFN-γ remained within acceptable limits in patients of both groups. However, the concentration of INT-γ was 2.5 times lower in patients with thyroid pathology (1.22±0.81 pg/ml) compared with patients with normal thyroid status (3.74±2.45

An increase in the level of IL-6 in patients with VTD up to 51.87±33.54 pg/ml in group 2 was established with its decrease by 2.5 times - up to 16.98±11.81 pg/ml in patients with FDTB and thyroid pathology. glands (group 3). The data obtained confirm the fact of an increase in the serum level of IL-6 in the majority of patients with active tuberculosis [26], which is a protective reaction to tuberculosis infection.

Discussion.

Thus, the results of the study demonstrate a change in the cytokine profile in patients with newly diagnosed widespread destructive forms of pulmonary tuberculosis, which is manifested by a significant increase in the levels of pro-inflammatory TNF-α, IL-6, as well as a moderate increase in the levels of IFN-γ and IL-2 and a decrease in the level of IL. The established change is a manifestation of the formation of an immune response to tuberculosis infection

and, therefore, is of a protective nature. However, in patients with impaired echostructure of the thyroid gland, significantly lower levels of pro-inflammatory cytokines TNF-α, IFN-γ, IL-2, IL-6 was noted in comparison with patients with unchanged echostructure of the gland, and the level of anti-inflammatory cytokine IL IL-4, on the contrary, higher in the group of patients with VTD with altered echostructure of the thyroid gland. These changes can be explained by a lower level of T4 in the systemic circulation of persons with thyropathies. At the same time, we have established a positive correlation between the level of T4 and the clinical severity of the process in persons with FDTB, more significant in patients with thyroid pathology.

In addition, a positive correlation was established between the values of the level of IL-6 and the values of the level of free T4 in both groups of patients with FDTB (respectively, $r = 0.375$; $p < 0.05$ in group 2 and $r = 0.463$; $p < 0.05$ in the group 3) with a more pronounced correlation in the group of tuberculosis patients with thyroid pathology. These data are consistent with the results of a positive correlation between IL-6 and T4 in hypothyroid patients with heart failure during L-thyroxine replacement therapy [17].

The proinflammatory cytokine of macrophage origin, IL-6, is synthesized by phagocytes, fibroblasts, T-lymphocytes of types 1 and 2, and endotheliocytes [25]. Although a number of studies have shown that IL-6 stimulates the intracellular growth of mycobacteria in monocytes [20,23], nevertheless, it has been proven that IL-6 is a key factor in the formation of resistance to tuberculosis [11]. Tuberculosis infection of IL-6 deficient mutated mice resulted in their lethality [19]. Thus, in patients with tuberculosis, an increase in the level of IL-6 is considered as a protective reaction.

When measuring the levels of total triiodothyronine and thyroxine and markers of immune status in healthy people of age, the concentrations of thyroid hormones were associated with inflammation markers, IL-6 expression by activated monocytes, and CD+T-lymphocyte receptors [11]. These data, as well as our results obtained in the examination of patients with tuberculosis, prove the fact that thyroid hormones regulate cytokine production. Analyzing the obtained results, one should also not neglect the data pointing to the feedback – activation of thyroid cells by some cytokines. In autoimmune thyroid diseases, the studied cytokines activate autoreactive T cells [4], and the administration of drugs that inhibit the production of TNF-α leads to an improvement in thyroid function in patients with hypothyroidism [18], which indicates the pathogenic role of the studied cytokines in thyroid dysfunction. It has been established that the administration of IL-6 to humans and experimental animals caused changes in thyroid function, which resembles the euthyroid syndrome with a decrease in TSH and T3 levels within 4 hours after administration [21,24]. IL-6 also reduces TSH-stimulated peroxidase mRNA expression and thyroid hormone secretion in vitro [22]. TNF-α and IL-6 are considered as mediators of low levels of thyroid hormones. Intravenous administration of TNF-α to healthy volunteers caused a decrease in T3 by 36% and an increase in T4 by 48% with a decrease in TSH by 68% within 12 hours [26]. In addition, high levels of TNF-α, which accompanied severe illness, were associated with a decrease in the activity of the 5'-deiodinase enzyme in the liver [15].

TNF-α mediates its biological effects through the activation of the transcription factor NF-[kappa]B. NF-[kappa]B activation plays a central role in generating immune and inflammatory responses by controlling gene expression of several cytokines. It was shown [16] that activation of the transcription factor NF-[kappa]B TNF-α suppresses T3-dependent induction of 5'deiodinase transfer RNA and enzymatic activity in liver cells. These results suggest that activation of the NF-[kappa]B transcription factor TNF-α may represent an important molecular link in the pathogenesis of the pathological euthyroid syndrome, where the underlying disease is associated with an increased level of TNF-α. Thus, the possibility of an inverse effect of elevated levels of IL-2, IFN-γ and, especially, IL-6 and TNF-α in patients with tuberculosis on their thyroid status cannot be ruled out. Tuberculosis intoxication, acting on the hypothalamic-pituitary-thyroid system, inhibits the production of thyroid hormone. At the same time, the level of cytokines, especially TNF-α and IL-6, which has sharply increased in response to tuberculosis infection, has a direct effect on the thyroid gland, causing the formation of antibodies (AT) to thyroperoxidase (TPO) and thyroglobulin (TG). These antibodies have a damaging effect on the thyroid gland [4], which leads to a further weakening of the production of thyroid hormones, an increase in the level of TSH and a compensatory increase in the volume of the gland (or its hypoplasia). At the same time, thyroid hormones are able to have a modulating effect on the production of immune mediators - cytokines, possibly through protein kinase-C [5].

Considering that in more than half of the examined patients with tuberculosis, we detected thyroid pathology in the form of a violation of its echostructure, a low level of T4 and an increased level of TSH in the systemic bloodstream, we draw attention to the need to screen the functional state of the thyroid gland in this contingent, because minimal thyroid

dysfunction with further progression leads to severe impairment of the functioning of various organs and systems [1,29]. In addition, the demonstrated correlations between the levels of thyroid hormone, certain cytokines, and the clinical severity of tuberculosis suggest the need for timely correction of thyroid dysfunction in order to restore the balance of cytokines and improve the outcomes of FDTB.

Conclusions.

1. For patients with newly diagnosed widespread destructive pulmonary tuberculosis, a slight decrease in the level of free thyroxine is characteristic, which indicates a weakening of the functional state of the thyroid gland and is a manifestation of the pathological euthyroidism syndrome characteristic of a number of severe systemic diseases.

2. In 51.16% of all patients with severe FDTB, a change in thyroid status was found, which is manifested by a change in the echostructure of the thyroid gland with signs of autoimmune thyroiditis and symptoms of subclinical (biochemical) hypothyroidism.

3. The severity of clinical manifestations of pulmonary tuberculosis negatively correlates with the level of free thyroxine in the systemic circulation, especially in the group of tuberculosis patients with thyroid pathology.

4. Common destructive forms of newly diagnosed pulmonary tuberculosis are accompanied by a significant increase in the levels of TNF-α and IL-6, some increase in the levels of IL-2, INT-γ and a decrease in IL-4 in the systemic circulation when compared with healthy individuals.

5. Thyroid pathology in patients with FDTB is combined with lower levels of all studied cytokines in the systemic circulation when compared with FDTB patients without thyroid pathology.

6. The data obtained reflect the close mutual influence of thyroid and cytokine profiles, as well as their participation in the formation of the inflammatory response to tuberculosis infection.

7. The established pattern justifies the timely screening of thyroid pathology in patients with pulmonary cavitary tuberculosis to restore thyroid homeostasis and cytokine balance.

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