рівнем експресії мРНК (mir-25) може стати фактором прогнозу перебігу захворювань, асоційованих з ВПЛ, зокрема «малих» форм уражень шийки матки, а також прогнозу ефективності медикаментозної терапії папіломавірусної інфекції, та вибору найбільш дієвих засобів імунотропного лікування.

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CYTOKINE PROFILE AND EFFICACY OF CHEMOTHERAPY DEPENDING ON THYROID STATE IN PATIENTS WITH PULMONARY TUBERCULOSIS

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Ключові слова: *туберкульоз легенів, щитоподібна залоза, імунітет, цитокіни*

Abstract. Cytokine profile and efficacy of chemotherapy depending on thyroid state in patients with pulmonary tuberculosis. Matvyeyeva S.L., Shevchenko O.S. *Objective of the study is definition of cytokine balance and the outcomes of chemotherapy of tuberculosis patients depending on their thyroid state. Materials and methods: 60 tuberculosis patients with pulmonary: 30 persons with unchanged thyroid gland and 30 persons with autoimmune thyroiditis and followed subclinical hypothyroidism were compared for the structure and the function of thyroid gland, cytokine balance and outcomes of antituberculosis chemotherapy. Thyroid glands of all patients were scanned 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 factor-α, interferon- γ and interleukins-2, -6, and -4 were measured. Outcomes of chemotherapy was estimated on the ground of general criterions: term and rate of stopping of bacilli excretion and healing of caverns in lungs. Results and discussion: In a comparative analysis of the data obtained, it was found that in tuberculosis patients with autoimmune thyroiditis and subclinical hypothyroidism compared with tuberculosis patients without thyroid pathology free thyroxine values in average decrease, the level of thyroid-stimulating hormone increases and levels of antibodies to both thyroglobulin and especially to thyroid peroxidase increase. In patients with concomitant autoimmune thyroiditis with subclinical thyroiditis, levels of pro-inflammation cytokines TNF-α, INF-γ, IL-2, IL-6 were significantly lower when compared with patients without thyroid pathology, and the level of anti-inflammation cytokine IL IL-4 was higher in a group of patients with autoimmune thyroiditis. Efficacy of chemotherapy was better in tuberculosis patients without thyroid pathology. These changes can be explained by a lower level of T4 in the systemic circulation of people with autoimmune thyroiditis and subclinical hypothyroidism. Conclusion: subclinical hypothyroidism accompanying concomitant autoimmune thyroiditis suppresses cytokine response in tuberculosis patients. That is followed worsening of treatment response during antituberculosis chemotherapy. Screening of thyroid state is recommended for TB patients for timely definition of thyroid pathology and its compensation if needed for improvement of the outcomes of antituberculosis chemotherapy.*

Реферат. Цитокіновий профіль та ефективність хіміотерапії залежно від тиреоїдного статусу хворих на туберкульоз. Матвєєва С.Л., Шевченко О.С. *Мета роботи: дослідження та визначення балансу цитокінів та результатів хіміотерапії хворих на туберкульоз залежно від стану щитоподібної залози. Матеріали та методи: порівнювали структуру та функцію щитоподібної залози, баланс цитокінів та результати протитуберкульозної хіміотерапії в 60 пацієнтів з легеневим туберкульозом: 30 осіб з незміненою щитоподібною залозою та 30 осіб з автоімунним тиреоїдитом та субклінічним гіпотиреозом. У всіх пацієнтів було проведено ультразвукове дослідження щитоподібної залози. Визначено рівень вільного тироксину, тиреотропного гормону гіпофізу та антитіл до тиреоглобуліну та тиреопероксидази в сироватці крові. Одночасно вимірювали рівень факторів некрозу пухлини-α, інтерферону-γ та інтерлейкінів-2, -6 та -4. Результати хіміотерапії оцінювалися на підставі загальних критеріїв: терміну та частоти припинення бактеріовиділення та загоєння каверн у легенях. Результати та обговорення: у порівняльному аналізі отриманих даних було встановлено, що у хворих на туберкульоз та автоімунний тиреоїдит з субклінічним гіпотиреозом порівняно з хворими на туберкульоз з незміненої щитоподібної залози значення вільного тироксину, у середньому, знижується, рівень тиреотропного гормону гіпофізу вірогідно підвищується, а рівень антитіл як до тиреоглобуліну, так і особливо до тиреопероксидази збільшується. У пацієнтів із супутнім автоімунним тиреоїдитом із субклінічним тиреоїдитом рівень протизапальних цитокінів TNF-α, INF-γ, IL-2, IL-6 був значно нижчим порівняно з пацієнтами без патології щитоподібної залози, а рівень протизапального цитокіну IL IL-4 був вищим у групі пацієнтів з автоімунним тиреоїдитом. Ефективність хіміотерапії була кращою у хворих на туберкульоз без патології щитоподібної залози. Ці зміни можна пояснити більш низьким рівнем Т4 у системній циркуляції хворих на автоімунний тиреоїдит із субклінічним гіпотиреозом. Висновки: субклінічний гіпотиреоз, що супроводжує автоімунний тиреоїдит, пригнічує відповідь цитокінів у хворих на туберкульоз. Наслідком цього є погіршення ефективності протитуберкульозної хіміотерапії. Скринінг стану щитоподібної залози рекомендується для хворих на туберкульоз для своєчасного визначення змінення функції щитоподібної залози та, якщо це необхідно, її компенсації для поліпшення результатів протитуберкульозної хіміотерапії.*

Acording to modern ideas, tuberculosis refers to interleukin-dependent immunodeficiency, accompanied by pronounced changes in the cytokine network of the body. Cells of the monocyte-macrophage system are activated by the thyroid gland in direct and indirect ways, which facilitates the elimination of the causative agent of tuberculosis from the body [2, 5, 7, 14].

Objective of the study is definition of cytokine balance and the outcomes of chemotherapy of tuberculosis patients depending on their thyroid state.

MATERIALS AND METHODS

60 patients with pulmonary tuberculosis (ТБ): 30 persons with unchanged thyroid gland (ТВ) (control group 1) and 30 ТВ patients with autoimmune thyroiditis and followed subclinical hypothyroidism (ТВ + АТ & SH) (group of observation 2) were compared for the structure and the function of thyroid gland, cytokine balance and outcomes of antituberculosis chemotherapy. The structure of thyroid was studied in both groups of patients by ultrasound scanning with diagnostic apparatus SSF-

240A by Toshiba Medical Systems production. The immunoassay of free thyroxine (T4 free), thyroid stimulating hormone (TSH), antibodies to thyroglobulin (at/TG) and thyroperoxidase (at/TPO) made with the reagents by the company "Ancor Bio" and spectrophotometer Tecan Sunrise [3] as well as immunoassay of some cytokines: tumor necrosis factor-α, interferon-γ, interleukin-2, -6, and -4 [8] made with the reagents by the company "Vector Best" were performed before and at the end of intensive phase of chemotherapy (after 60 daily doses of standardized regimens).

Treatment response of antituberculosis chemotherapy was estimated on the ground of general criterions like rate and term of stopping of bacilli excretion and of reducing the sizes of tuberculosis caverns in lungs.

RESULTS AND DISCUSSION

Patients of control group had normal volume and echotexture of thyroid gland. Thyroid glands of TB patients with autoimmune thyroiditis (AT) had mainly diffusely enlarged thyroid glands with heterogeneous echotexture with presence of hypoechoic micronodules (1-2 mm) with surrounding echogenic septations. Color Droppler study in most cases showed normal or decreased flow. In 3 cases large nodules were present which may be referred as nodular Hashimoto thyroiditis [1].

When studying the hormonal profile in most TB patients of control group with normal thyroid (group 1), low normal values of free T4 (12.71±0.98) pmol/ml were revealed. In patients with TB and AT (group 2), this indicator dropped to the borderline value and amounted to (11.21±0.67) pmol/l. When compared the average values of free thyroxin in 2 months after starting the treatment (at the end of intensive phase), a significant decrease in its level in a group of patients with AT from (10.43±0.85 to 8.12±0,80) pmol/l and unsignificant decrease was found in group 2 (from 11.21±0.67 to 10.43±0.85) pmol/l (table 1).

The level of thyroid-stimulating hormone in the systemic blood flow in the control group 1 of patients with a normal echotexture of the thyroid gland was within the physiological normal value (1.29±0,78) mIU/ml and slightly increased (1.80±0.94) mIU/ml to the end of the intensive phase of antituberculosis chemotherapy. The level of TSH in the group-2 of TB patients with the AT significantly increased to pathological value and increased more from (4.20±1,41) to (4.80±1,52) mIU/ml to the end of intensive phase. Subclinical hypothyroidism was present in patients of group 2 judging on the level of T4 free which was minimal and TSH which was more than 4.2 mIU/ml. Hypothyroidism worsened to the end of intensive phase. Thus antituberculosis treatment leads to the suppression of thyroid function.

Table 1

Indexes of thyroid profile in TB patients depending on echotexture of thyroid gland

Index	Group1 (TB) (n=30)		Group 2 (TB+ AT & SH) (n=30)	
	before treatment	after 60 doses	before treatment	after 60 doses
T4free (pmol/l)	11.21±0.67	10.43±0.85	10.43±0.85 $p_{1,2}>0,05$	8.12±0,80 $p_{1,2}<0,05$
TSH (mcIU/ml)	1.29±0,78	1.80±0.94	4.20±1,41 $p_{1,2}>0,05$	4.80±1,52 $p_{1,2}<0,05$
at/TG (U/ml)	5.38±1,91	6.55±1.2	18.45±1.83 $p_{1,2}<0,05$	38.54±1.27 $p_{1,2}<0,05$
at/TPO (U/ml)	3.24±0,39	4.41±0.94	380.54±1.27 $P_{1,2}<0,05$	430.22±1.63 $P_{1,2}<0,05$

Levels of antibodies to thyroglobulin, as well as to thyroid peroxidase did not exceed the normal allowable values in control group 1. The content of antibodies to TG was (5.38±1.91) U/ml before starting the treatment and (6.55±1.2) U/ml to the end of intensive therapy. The content of antibodies to TPO was (3.24±0,39) U/ml before starting the treatment and (4.41±0.94) U/ml to the end of intensive therapy. But both indicators significantly increased in the group 2 of TB patients with autoimmune thyroiditis compared with the control group 1. TG in the group of TB patients with autoimmune thyroiditis significantly increased previously to (18.45±1.83) U/ml with further increasing to the end

of intensive therapy to (21.54±1.18) U/ml. The concentration of antibodies to TPO in these patients was (380.54±1.27) U/ml and significantly increased to (430.22±1.63) U/ml to the end of the intensive therapy. Thus, autoimmune disease in patients of the group of observation was confirmed both by geterogenous texture of thyroid and by increased level of antibodies to thyroperoxidase.

So, in a comparative analysis of the data obtained, it was found that in tuberculosis patients with autoimmune thyroiditis and subclinical hypothyroidism compared with tuberculosis patients with unchanged thyroid gland free thyroxine values in average decreases, the level of thyroid-stimulating hormone increases and levels of antibodies to both thyroglobulin and especially to thyroid peroxidase increase. These pathological changes worsened during antituberculosis chemotherapy.

When studying the cytokine profile in a group of patients with TB + AT & SH, a significant decrease in the levels of TNF-α, INT-γ compared to the control, as well as a moderate decrease in IL-2 and IL-6, and an increase in the level of IL-4 compared to the control were established (table 2). In TB patients with AT & SH, the level of TNF-α was 30.77±16.77 pg/ml, which is half the values in patients with normal thyroid status (60.84±25.01 pg/ml).

The concentration of INT-γ was 2.5 times lower in patients with autoimmune thyroiditis and subclinical thyroiditis (1.22±0.81 pg/ml) when compared with patients maintaining normal thyroid status (3.74±2.45 pg/ml). Given the lower values of T4 in patients with tuberculosis with thyroid pathology, and the indication that thyroxin is a potential inducer of INF-γ [4, 6], it can be assumed that the production of INF-γ is related to the level of thyroxine in the systemic circulation in patients with TB and AT.

The content of IL-2 in the systemic blood flow of TB patients without thyroid pathology remained within the allowed physiological values (7.08±1.97 pg/ml) with a decrease of 2.5 times in TB patients with autoimmune thyroiditis (4.88±1,05 pg/ml).

The content of IL-6 in TB patients with autoimmune thyroiditis 3 times lower when compared with TB patients without thyroid pathology – relatively (16.98±1.81) and (51.87±3.54) pg/ml. The obtained data confirm the fact of an increase in serum IL-6 level in the majority of patients with active tuberculosis [10], which is a protective reaction to tuberculosis infection.

Table 2

The levels of cytokines in free bloodstream in TB patients depending of thyroid pathology

Groups	TNF-α, pg/ml	INT-γ, pg/ml	IL-2, pg/ml	IL-6, pg/ml	IL-4, pg/ml
Group1(TB); n=30 before treatment	**60.84±5.01**	**3.74±2.45**	**7.08±1.97**	**51.87±3.54**	**0.002±0,003**
in 2months	**68.56±4.19**	**4.12±1.59**	**8.11±2.02**	**60.65±3.24**	**0.003±0,004**
Group 2 (TB+ AT & SH); n =30 before treatment	**30.77±6.77**	**1.22±0.81**	**4.88±1.05**	**16.98±1.81**	**0.040±0,019**
in 2months	**31.23±5.94**	**1.59±0.83**	**5.09±1.11**	**17.07±1.67**	**0.071±0,009**
$p_{1,2}$ (before treatment)	**<0,05**	**<0,05**	**<0,05**	**<0,05**	**<0,05**
$p_{1,2}$ (in 2months)	**>0,05**	**>0,05**	**>0,05**	**<0,05**	**>0,05**

Levels of IL-4 in TB patients with AT & SH increased compared with the control group 1. Lower values of this indicator were observed in persons with thyroid gland pathology and were (0.002±0.003) pg/ml in group 1 and (0.040±0,019) pg/ml in group 2, respectively. Obtained data are apparently due to a significant increase in the level of IL-6, which is an antagonist of IL-4, which inhibits secretion by macrophages of IL-6. Decreased secretion of IL-4 increases the resistance of the body to tuberculosis infection and, thus, is a protective event in the formation of an immune response in patients with tuberculosis.

At the end of the intensive phase of therapy no significant changes in cytokine profile was occurred (table 2).

Thus, the results of the study demonstrate a change in the cytokine profile in patients with 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 INF-γ and IL-2 and a decrease in IL-4. The established change is a manifestation of the formation of an immune response to a tuberculosis infection and is thus of a naturel protector. However, in patients with concomitant autoimmune thyroiditis with subclinical thyroiditis, levels of pro-inflammation cytokines TNF-α, INF-γ, IL-2, IL-6 were significantly lower when compared with patients without thyroid pathology, and the level of anti-inflammation cytokine IL IL-4 was higher in a group of patients with autoimmune thyroiditis. Efficacy of chemotherapy was better in tuberculosis patients without thyroid pathology. These changes can be explained by a lower level of T4 in the systemic circulation of people with autoimmune thyroiditis and subclinical hypothyroidism. The proinflammation cytokine of macrophage origin IL-6 is synthesized by phagocytes, fibroblasts, T-lymphocytes of types 1 and 2 and endotheliocytes [12]. Although a number of studies have shown that IL-6 stimulates intracellular growth of mycobacteria in monocytes [11, 13], nevertheless, it has been shown that IL-6 is a key factor in the formation of tuberculosis resistance [4]. Tuberculosis of mutated mice with IL-6 deficiency led to their lethality [9]. Thus, in patients with tuberculosis, an increase in the level of IL-6 is considered as a protective reaction.

When measuring total triiodothyronine and thyroxine levels and markers of immune status in healthy people at the age of concentration, thyroid hormones were associated with inflammation markers, IL-6 expression by activated monocytes and CD + T-lymphocyte receptors [7]. These data, as well as our results obtained by examining patients with tuberculosis, prove the fact of regulation cytokine production by thyroid hormones.

Table 3

Estimation of treatment response of TB patients at the end of intensive therapy depending on thyroid state

Groups	Stopping of bacilli excretion			Reducing of the cavitation		
	n		Term (months)	n		Term (months)
	absolute	%		absolute	%	
Group1(TB) n=30	24	79.77	1,71±0,08	23	76,66	2,58±0,08
Group 2 (TB+ AT&SH) n =30	20	66.66*	2,20±0,14*	18	60,00*	3,11±0,15*

N o t e : * the intergroup value is significantly different, p <0.05.

At the end of intensive therapy treatment response in TB patients with normal thyroid state (control group 1) was better compared with TB patients with AT & SH judging on the ground of rates and terms of stopping of bacilli excretion and reducing of the cavitation in size (table 3).

CONCLUSIONS

Subclinical hypothyroidism accompanying concomitant autoimmune thyroiditis suppresses cytokine response in tuberculosis patients. That is followed worsening of treatment response during antituberculosis chemotherapy. Screening of thyroid state is recommended for TB patients for timely definition of thyroid pathology, especially of the suppression of its function and its compensation if needed for improvement of the outcomes of antituberculosis chemotherapy.

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