



## IMMUNOPATOLOGICAL ASPECTS IN PATIENTS WITH FIRST DETECTED PULMONARY TUBERCULOSIS

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Article history:	Abstract:
<p><b>Received:</b> September 3<sup>rd</sup> 2021 <b>Accepted:</b> October 4<sup>th</sup> 2021 <b>Published:</b> November 28<sup>th</sup> 2021</p>	<p><b>Relevance:</b> Throughout the world the epidemiological situation with regard to tuberculosis remains difficult.</p> <p><b>Purpose of the study:</b> to study the immunobiological features of the organisms in newly diagnosed patients with pulmonary tuberculosis.</p> <p><b>Materials and research methods:</b> A comprehensive examination was carried out on 160 first diagnosed tuberculosis and 66 patients with relapsed tuberculosis. All patients underwent general clinical, bacterioscopic examination, chest X-ray. The concentration of cytokines – tumor necrosis factor-<math>\alpha</math> (TNF-<math>\alpha</math>), C-reactive protein (CRP) and vasculo-endothelial growth factor (VEGF) were determined.</p> <p><b>Conclusions:</b> A moderate increase in the level of CRP allows early detection of the course of the pathological process and ascertains the formation of a systemic inflammatory response to activate phagocytosis. It was estimated that there is a correlation at decreasing of TNF-<math>\alpha</math> concentration in the blood serum in secondary patients with recurrent tuberculosis by increasing the level of VEGF in the same patients.</p>

**Keywords:** Pulmonary Tuberculosis, Immunity, Cytocynes.

### RELEVANCE:

Throughout the world the epidemiological situation of tuberculosis disease among the other infectious diseases remains difficult. Understanding the pathogenetic mechanisms of development of the inflammatory response in different variants of the tuberculosis course is necessary prerequisite for increasing the effectiveness of prevention and treatment in patients with tuberculosis by targeting these mechanisms. The body's defensive response to infection, including MBT, manifests itself in the form of a systemic inflammatory reaction syndrome, which is currently under the close scrutiny of many researchers around the world.

### PURPOSE OF THE STUDY:

Study of immunobiological properties of the organism in newly diagnosed patients with pulmonary tuberculosis.

### MATERIALS AND METHODS:

In order to study the clinical course of pulmonary tuberculosis in newly diagnosed patients and increase the effectiveness of treatment, a comprehensive examination was carried out in 160 patients with newly diagnosed tuberculosis and 66 patients with relapsed tuberculosis aged from 17 to 70 years.

All patients were underwent general clinical examination, bacterioscopic examination of sputum smear on MBT according to Ziehl-Neelsen, sputum culture and plain chest X-ray. Methods MGIT, Hien test (Genotype INA and Genotype RMP), Gene Xpert/RIF were used as an express method and determination of MBT genotypes.

The concentration of cytokines - TNF- $\alpha$ , CRP and VEGF in blood serum was determined with biochemical methods.

### RESULTS:

Results were distributed by age and gender. Among the newly diagnosed patients, persons aged from 21 to 40 years (50.5%) prevailed among men, and among women – more younger ones - 21-30 years old (36.4%). In general, tuberculosis often affects the most able-bodied and reproductive part of the population (from 20 to 60 years old), which causes significant economic damage to the state.

Among the patients with relapses, men predominated, especially at the age of 31-50 years (64.5%), a relapse of pulmonary tuberculosis occurred in women aged 17-30 (23.1%) and over 51 years (33.7%).

The distribution according to clinical forms of the disease among newly diagnosed patients with pulmonary tuberculosis was as follows: more than a third were diagnosed with infiltrative forms of the



process - 67.5%, then in terms of frequency of occurrence - focal pulmonary tuberculosis - 13.7%, disseminated - in 6.9% and fibrous-cavernous pulmonary tuberculosis (FCT) - in 3.75% of patients. Other forms of tuberculosis (tuberculous pleurisy, cavernous, tuberculoma, caseous pneumonia) were less common - in 7.9% of cases.

When it comes to groups, distributed according to clinical forms of the disease among patients with recurrent pulmonary tuberculosis, attention is drawn to the rapid increase in patients with fibrous-cavernous pulmonary tuberculosis - 36.6%, infiltrative tuberculosis was 43.9%. Focal, cavernous and disseminated pulmonary tuberculosis occurred in 4.5%, cirrhotic and tuberculoma in 3% of cases.

Amongst the newly diagnosed patients, concomitant diseases were detected in 66 patients (41.25%). Of these, the most common: HIV infection - in 14 (15.4%) cases, diabetes mellitus - in 18 (31.8%) cases, chronic nonspecific lung diseases and anemia, respectively in 19 and 41 (12.1% and 25.8%) cases [1-8].

Concomitant diseases were identified in 44 (66.7%) patients with relapsed tuberculosis. Of these, diabetes mellitus in 17 (38.6%) cases, anemia - in 11 (25%) cases, drug addiction and HIV infection - in 10 (22.7%) and 7 (15.9%) cases respectively, chronic nonspecific lung diseases in 5 (11.4%) and hepatitis - in 7 (15.9%) of patients.

118 (73.7%) patients with newly diagnosed TB, upon admission, had a relatively satisfactory condition. 22 (13.7%) patients were admitted in a state of moderate severity and 12 (7.5%) - in a serious condition, 8 patients were admitted in a satisfactory condition, and these patients were identified during a preventive examination.

Half of the patients with recurrent pulmonary TB had - 16 (24.4%) moderate condition and 17 (25.8%) severe condition on admission; another half of the patients (50%) had a relatively satisfactory condition.

The study of factors contributing to the development of pulmonary tuberculosis revealed in 88 (64 ± 4.1%) cases the predominance of the value of the social factor [9-16].

In the group of patients with recurrent pulmonary TB, the influence of the social factor increased to 48 (73 ± 4.1%) cases.

Symptoms of severe intoxication were noticed in both newly diagnosed pulmonary TB patients and patients with recurrent TB: severe weakness in 124 (96.9 ± 1.5%) patients, fever up to 38°C and higher in 123 (96.1 ± 1.7%), decreased appetite in 117 (91.4 ± 2.5%), increased sweating in 112 (87.5 ± 2.9%), weight loss in 111 (86.7 ± 3.0%), palpitations in 101

(78.9 ± 3.6%), headache in 76 (59.4 ± 4.3%) and chills in 60 (46.9 ± 4.4%) patients.

Bronchopulmonary symptoms among patients with newly diagnosed pulmonary TB were observed in 124 patients. Thus, 124 (77.5 ± 2.5%) patients had a persistent cough (106 of which (66.25 ± 3.3%) had sputum), 46 (28.75 ± 4.4%) - chest pain, in 44 (27.5 ± 4.3%) - shortness of breath (to varying degrees). Often, bronchopulmonary symptoms were manifested by periodic hemoptysis in 17 (10.9 ± 2.8%) and bleeding in 5 (3.1 ± 1.3%) cases.

Bronchopulmonary symptoms in patients with relapsed tuberculosis were more pronounced and occurred in 55 patients. Of these: 53 (80.3 ± 2.5%) patients had a persistent cough with sputum, 16 (24.2 ± 4.4%) had chest pain, 32 (48.5 ± 4.3%) - shortness of breath (to varying degrees). Often, bronchopulmonary symptoms were manifested by periodic hemoptysis in 9 (13.6 ± 2.8%) and bleeding - in 3 (4.5 ± 1.3%) patients.

The study of the hemogram showed the presence of leukocytosis - in 57 (44.6 ± 4.4%) cases of patients with newly diagnosed pulmonary TB and in 33 patients with relapsed TB. Segmented neutrophilia - 37 (28.9 ± 4.0%), stab neutrophilia - 53 (41.4 ± 4.3%), lymphopenia - 70 (54.7 ± 4.4%), monocytosis - 18 (14, 1 ± 3.1%), ESR increased in 125 (97.7 ± 1.3%) patients.

X-ray examination showed that in 108 (67.5 ± 4.2%) cases, among the newly diagnosed patients, a one-sided process was noted and in 52 (32.5 ± 4.2%) cases - a two-sided one. In 102 (63.7 ± 3%) patients, the presence of destructive changes with dissemination and severe infiltration was revealed [17-25].

In patients with recurrent pulmonary tuberculosis bilateral process prevails in 30 (64.8 ± 4.2%) patients with destructive changes. Dissemination and severe infiltration were prevailed in 55 (83.3 ± 3%) patients.

An important point of the present study was the comparison of the growth time of MBT colonies in a culture study isolated from newly diagnosed and from patients with recurrent tuberculosis. For those newly identified, the presence of fast-growing MBT is more characteristic. In 72 (80%) samples, a magnificent - eignonic growth of colonies was noted on 10-14 days of sowing, and in 18 (20%) - on 25-30 days and the growth of colonies was scarce.

MBT with recurrent tuberculosis in 12% of cases did not give visible growth until 20-25 days, in 62 (88.6%) cases the growth of colonies was noted from 30-35 days of sowing, which indicates the presence of slow-growing MBT in patients with recurrent tuberculosis, who have previously received anti-tuberculosis therapy. The growth of MBT culture



in patients with recurrent tuberculosis was on average 2 weeks behind than in those newly diagnosed.

In epidemiological terms, the most dangerous were 56 (59%) newly diagnosed patients in whom MBT was detected by the method of bacterioscopy. In 79 (83.2%) patients MBT was detected by bacteriological method. The total number of bacteria excreting among the newly diagnosed patients was 95 (59.4%) patients.

Among the patients with relapsed tuberculosis process, bacterial excretion was found in 36 patients (54.5%). Of these, 18 (50%) MBT were detected by the bacterioscopy method and 24 (66.7%) by the bacteriological method.

As a result of a study on the sensitivity to anti-tuberculosis drugs, in 15 (22.7%) cases patients with relapses showed the presence of resistant strains of MBT. This category of patients was taken for treatment according to category IV.

42 (63.6%) patients in whom MBT were sensitive to first-line drugs were treated according to category (II) and 9 patients (13.7%) were treated according to an individual scheme with first-line drugs.

An individual treatment regimen was developed due to the intolerance of antibacterial drugs due to the presence of concomitant diseases. It should be noted that category II and individualized treatments were prescribed based on the results of bacteriological studies carried out by express methods (Hien-test (Genotype INA and Genotype RMP), Gene Xpert/RIF). Such treatment was carried out due to the late response of the study results, which takes an average of 3 months, using the Levenshtein – Janssen method.

As a result of a study on sensitivity to anti-tuberculosis drugs, in 7 (4.4%) cases among newly diagnosed patients, the presence of resistant strains of MBT was noted. This category of patients was initially admitted to category IV treatment. One patient was transferred to category II treatment because of the high prevalence of the process and the low effectiveness of treatment in category I. The remaining 152 (95%) patients were taken for treatment in category I.

It should be noted that treatment in the first category was prescribed based on the results of bacteriological studies carried out by express methods [Hien test (Genotype INA and Genotype RMP), Gene Xpert/RIF].

We conducted a study for the presence of prognostically and diagnostically significant markers in blood serum in 30 patients with a verified diagnosis of pulmonary tuberculosis. Comparative group is 15 practically healthy people. Of the 30 examined patients: 7 (23.3 ± 7.7%) were women, 23 (76.7 ± 7.7%) were men; the average age for women is 40.5

± 3.18 years, for men - 47.1 ± 2.38 years. Focal pulmonary tuberculosis was verified in 7 (23.3 ± 7.7%) patients, infiltrative tuberculosis in 14 (46.7 ± 8.9%), fibrous-cavernous tuberculosis in 6 (20.0 ± 7.7%), cavernous tuberculosis in 2 (6.7 ± 2.2%); and 1 (3.3 ± 1.2%) had tuberculous bronchoadenitis. The patients were divided into 2 groups: group 1 - newly diagnosed patients (13 people - 43.3 ± 9.0%); group 2 - those who reapplied with a relapse of the disease (17 people - 56.7±9.0%); Group 3 - 15 practically healthy people.

In all studied patients, quantitative determination of prognostically and diagnostically significant markers - C-reactive protein (CRP), endothelial vascular growth factor VEGF and alpha-TNF (tumor necrosis factor) - was carried out.

Results of CRP determination in newly diagnosed (group 1) and in patients with relapse (group 2) of pulmonary tuberculosis: compared with healthy people (concentration of CRP 3-5 mg/l), the newly diagnosed patients showed a significant increase in the content of the marker in the blood serum (28.69 ± 0.74 mg/l,  $p < 0.05$ ). In patients with a relapse of the disease, the level of CRP was statistically significantly lower than in newly diagnosed patients with pulmonary tuberculosis (5.42 ± 2.73 mg/l,  $p < 0.05$ ), and corresponded to the background values of healthy people.

Compared with healthy people (VEGF concentration 100-200 pg/ml), all studied patients showed a significant increase in the content of the marker in the blood serum. At the same time, in patients with a relapse of the disease, the VEGF level was statistically significantly higher than in newly diagnosed patients with pulmonary tuberculosis (847.0 ± 182.3 pg/ml and 505.76 ± 103.06 pg/ml, respectively,  $p < 0, 05$ ).

Results of TNF- $\alpha$  determination in newly diagnosed and patients with recurrent pulmonary tuberculosis: compared with healthy people (concentration of TNF- $\alpha$  0.5-1 pg/ml), all studied patients showed a significant increase in the content of the marker in the blood serum [26,27]. At the same time, in patients with a relapse of the disease, the level of TNF- $\alpha$  was statistically significantly lower than in newly diagnosed patients with pulmonary tuberculosis (1.72 ± 0.24 pg/ml and 11.92 ± 2.49 pg/ml, respectively,  $p < 0.05$ ). It should be noted that there is a direct relationship between VEGF and TNF- $\alpha$  levels. VEGF expression is induced by pro-angiogenic factors, in particular cytokines. Thus, a decrease in the serum TNF- $\alpha$  concentration in patients with a relapse of the disease (group 2) directly correlates with an increase in the VEGF level in the same patients. Determination of the TNF- $\alpha$  marker in the blood serum of patients with pulmonary tuberculosis



should be carried out in parallel with the detection of VEGF expression, which can serve as a diagnostic and prognostic sign for early detection of a pathological process.

### CONCLUSIONS:

A moderate increase in the level of CRP in initially diagnosed patients with pulmonary tuberculosis was found within the range of no more than 30-40 mg/l, which allows early detection of the course of the pathological process and ascertain the formation of a systemic inflammatory response to activate phagocytosis.

It was estimated that there is correlation at decreasing of TNF- $\alpha$  concentration in the blood serum in secondary patients with recurrent tuberculosis by increasing of the level of VEGF in the same patients. Determination of the TNF- $\alpha$  marker in the blood serum of patients with pulmonary tuberculosis should be carried out in parallel with the detection of VEGF expression, which increases the diagnostic and prognostic value of the studied markers for early detection of the pathological process.

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