

Diagnostic Features of Drug-resistant Pulmonary Tuberculosis in Adults in Lviv Region, Ukraine

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doi: 10.71168/NMP.02.02.126

Received Date: January 30- 2026

Publication Date: February 25- 2026

Abstract

Aim: The aim of the work is to study the clinical and laboratory features of the diagnosis of drug-resistant pulmonary tuberculosis (DR-PTB) in adults.

Materials and Methods: 184 medical files of patients with TB were analyzed. The main group consisted of 134 people who developed DR-PTB, and the control group consisted of 50 patients with susceptibility pulmonary tuberculosis (S-PTB).

Results and Discussion: The clinical and radiological course of the specific process depends on the susceptibility/resistance of *Mycobacterium tuberculosis*. The disseminated form was diagnosed 1.5 times more often, fibrous-cavernous 1.7 times more often and 2.2 times less often infiltrative form of DR-PTB compared to S-PTB. The progression was observed 3.7 times caseous pneumonia and bronchial TB 1.9 times more often. The using of sputum polymerase chain reaction for detection of MBT contributed to timely diagnosis of DR-PTB in 94.0%. In the majority of patients (94.7%) of the main group, an increase in ESR was noted. Moreover, an increase in ESR over 31 mm/h was detected in 23.8%, leukocytosis in 30.6%, eosinopenia in 31.3%, lymphopenia in 58.9%, lymphocytosis in 40.3%. High levels of C-reactive protein were found in 70.9% of patients from the main group and 2.4 times less often in control patients. A 1.2-fold decrease in the phagocytic index, a 2.5-fold in the phagocytic number; a 1.3-fold decrease in the content of unfermented cationic lysosomal proteins of granulocytes, and an immunoregulatory index were found in DR-PTB. The population of T-suppressors increases by 1.2 times, and number of T-helpers decreases by 1.2 times. The tumor necrosis factor- α increased by 2.7 times, IL-6 by 1.9 times in main group.

Conclusion: The present study indicates the importance of comprehensive clinical and laboratory diagnostics of DR-PTB to determine the features of the course of a specific process and the appointment of optimal antimycobacterial therapy.

Keywords: Diagnosing, Drug-resistant tuberculosis, Immunity, Laboratory parameters.

Introduction

Tuberculosis is a serious infectious disease caused by *Mycobacterium tuberculosis* (MBT), which is transmitted from person to person by airborne droplets [1]. Tuberculosis (TB) usually affects the lung parenchyma, but can also affect other organ systems, such as the brain, kidneys, or spine. Drug-resistant forms of pulmonary TB (PTB) often arise in modern conditions. This complicates the treatment process and increases the risk of further spread of the disease among the population [2,3,4].

The use of an outdated approach to the detection and diagnosis of TB remains widespread in Ukraine, but despite the availability of a regulatory framework that allows the use of international World Health Organization (WHO) guidelines for the diagnosis and treatment of TB.

The implementation of a two-week empirical treatment with antibiotics for the differential diagnosis between TB and pneumonia instead of sputum polymerase chain reaction (PCR) for the detection of MBT significantly increases the time to determine the etiology of the process [5,6]. On the background of an increase in the frequency of resistant forms of the specific process, the pathomorphosis of TB occurs [7,8]. There have been several new developments in the diagnosis and treatment of drug-resistant TB (DR-PTB), and this progress continues over the past decade. Rapid molecular diagnostic methods that can detect both the pathogen and its susceptibility/resistance have become widely available and their capabilities are rapidly expanding. There is an urgent need to improve culture methods to facilitate diagnosis, especially in vulnerable populations [6].

The central link in anti-tuberculous protection is the interaction of immunocompetent cells bearing the CD4+ marker and cytolytic CD8+ lymphocytes. Stimulated CD4+ lymphocytes (Th-1) secrete macrophagotropic cytokines that activate phagocytosis by macrophages and monocytes [9].

Therefore, the analysis of literature data indicates the importance of comprehensive clinical and laboratory diagnostics of DR-TB for timely diagnosis, determination of the features of the course of a specific process, and application of optimal antimycobacterial therapy (AMBT) regimens [5,6].

Considering the above, for the timely detection of DR-PTB, it is justified to use a multimodal clinical and laboratory study, which includes: general laboratory, microbiological, biochemical and immunological diagnostic methods, etc. However, the role of a comprehensive clinical and laboratory examination of patients with DR-PTB is not fully covered in the literature, the difference in immune system indicators depending on the sensitivity/resistance of MBT strains to antimycobacterial drugs (AMBDs) and their diagnostic value in these patients is not sufficiently defined.

The aim of the work is to study the clinical and laboratory features of the diagnosis of CR-PTB in adults.

Materials and Methods

184 medical files of patients with active TB were retrospectively analyzed. The main group of patients consisted of 134 people who developed DR-PTB. The control group consisted of 50 patients with sensitive pulmonary tuberculosis (S-PTB). At the same time, based on the results of the drug susceptibility test (DST), it was found that 107 patients isolated MBT resistant to first-line drugs and 27 to reserve drugs, including fluoroquinolones. All patients were diagnosed with a new case of TB and all of them were treated in anti-TB hospital of the Lviv region. Patients received treatment depending on the DST indicators.

We study the radiological features of PTB. The following procedures were performed: survey radiography in direct and lateral projections of the chest organs, tomographic examination in different sections, computed tomography of the chest organs, and fiberoptic bronchoscopy (according to indications).

All patients underwent microbiological examination of sputum for the presence of MBT, as well as sensitivity/resistance of MBT strains to AMBDs of the first and second lines. Microbiological examination included: rapid molecular genetic tests for the detection of MBT susceptibility to AMBDs (GeneXpert MBT/RIF and linear probe tests, such as GenoType MBTDRplus and GenoType MBTDRsl), smear microscopy, culture of material on Lowenstein-Jensen medium and typing of isolated MBT on BACTEC MGIT 960, with DST [10].

A general clinical blood test was performed to determine the level of hemoglobin, erythrocytes, total leukocytes and their fractional composition (myelocytes, metamyelocytes, rod-shaped, segmented neutrophils, eosinophils, basophils, lymphocytes, monocytes), erythrocyte sedimentation rate (ESR). The blood examination was performed on an automated hematological analyzer MicroCC-18 (High Technology Inc.). In some cases subpopulations of leukocyte cells were also determined manually by a unified method of morphological examination of blood cells with differential leukocyte formula counting.

The examination of the state of phagocytic, T- and B-cells and anti-tuberculous immunity was analyzed in 25 patients with newly diagnosed DR-PTB and 22 patients with S-PTB.

The parametric (variational) statistics methods were used in compliance with the conditions for assessing the type of distribution for statistical processing of the researched data. The results are presented in the form of the average statistical value of the indicator and the error of the mean $M \pm m$. The reliability of the results obtained was assessed using the Student and Mann-Whitney test. Statistical processing of the data was carried out using the STATISTICA 2006 computer software package.

Results and Discussion

The sample of patients was dominated by men, who were 3.8 times more numerous (108; 80.5%) than women (26; 19.4%). Men were more often ill at the age of over 30 years (92.9%, ($p < 0.05$)). At the same time, among women, the largest number of patients (56.7%) were in the age range of 20-29 years, after 30 years the number of cases decreased by 4 times.

The clinical and radiological methods of diagnosing

In a comparative assessment of the clinical and radiological course of sensitive and drug-resistant PTB, it was found that in patients with DR-PTB, disseminated TB was diagnosed 1.5 times (67.3% vs. 44.0% ($p < 0.05$)) and fibro-cavernous TB 1.7 times more often (10.4% vs. 6.0% ($p < 0.05$)) than in patients with S-PTB. At the same time, the infiltrative form of PTB was diagnosed 2.2 times less often in the main group than in the control, Table 1. The destructive process was 1.5 times more often observed in patients with DR-PTB (94.5 ± 0.9 vs. 61.5 ± 0.8)%.

Table 1: Distribution of patients in the main and control groups according to clinical forms of tuberculosis and the presence of destruction in the pulmonary parenchyma.

Radiological forms of pulmonary tuberculosis	The control group (n = 50)			The main group (n = 134)		
	All abs.n/(%)	Destruction +		All abs.n/(%)	Destruction +	
		abs.n	(%)		abs.n	(%)
The infiltrative	25 (50.0)	10	40.0	30 (22.3)*	22	90.4**
The disseminated	22 (44,0)	10	44,5	90 (67,3)*	84	93,3**
The fibro-cavernous	3 (6,0)	3	100	14 (10,4) *	14	100
Average indicator		7,6 \pm 0,4	61,5 \pm 0,8*		70,4 \pm 0,8	94,5 \pm 0,9**

Note: * significant difference compared to the control group, $p < 0.05$; ** significant difference compared to the control group, $p < 0.05$.

The gradual onset of a specific process in the lungs was noted in 70 (52.2%) patients, acute in 64 (47.8%) patients of the main group. At the same time, the acute course in the control group was noted 1.5 times more often than in the main group.

In 76.8% (out of 184) of the examined patients, changes in the lungs were detected when consulting a family doctor. The duration of the disease was more than a year in most of the cases (66.4%) of the main group, compared to the control, and on average (10.5 ± 1.5) months vs. (5.1 ± 1.0) months ($p < 0.05$). At the same time, in 94.7% (127) of DR-PTB, pronounced symptoms of tuberculous intoxication were noted, and in 57.4% (77) symptoms of lung damage, accompanied by respiratory failure in 97 (72.4%) of the patients in the main group.

The laboratory methods of diagnosing

In the case of DR-PTB, the majority of patients (95.5%) had an increase in ESR. Its increase was more than 31 mm/h detected in 28.3% (38) of patients, which is significantly more common than in the case of S-PTB (14.0%). Also, in the patients of the main group, leukocytosis was observed more often (30.6% vs. 18.0%; ($p < 0.05$)), eosinopenia 31.3% vs. 12.6% ($p < 0.05$), and eosinophilia with almost the same frequency. Lymphopenia was found in 58.9% (79) of patients with DR-PTB, which is three times more common than in sensitive, lymphocytosis 2.8 times (40.3% vs. 14.0%, respectively ($p < 0.01$)).

From the culture study of sputum, it was established that massive bacterial excretion was significantly more often (2 times) observed in patients with DR-PTB (75.8% vs. 33.3%, $p < 0.05$) than in patients with S-PTB. In patients with DR-PTB, progression of the tuberculous process was observed more often than in controls, Table 2. In particular, caseous pneumonia was diagnosed 3.7 times (22.3% vs. 6.0%, ($p < 0.01$)), bronchogenic rejection 2.2 times (74.6% vs. 34.0%) ($p < 0.05$), bronchial TB 1.9 times (26.8% vs. 14.0%) ($p < 0.05$) more often in patients of the main group, compared to the control. However, exudative pleurisy was diagnosed 3.1 times more often in the control group (30.0% vs. 9.7%) ($p < 0.01$) of the examined. At the same time, bone TB and abdominal TB were observed in isolated cases of both groups.

Table 2: Frequency and nature of specific and nonspecific complications of tuberculosis in individuals of the studied groups.

Type of complications	The control group (n=50)		The main group (n=134)		p
	abs.n.	%	abs.n.	%	
The caseous pneumonia	3	6.0	30	22.3	<0.01
The bone TB	1	2.0	3	2.2	>0.05
The abdominal TB	1	2.0	4	2.9	>0.05
The exudative pleurisy	15	30.0	13	9.7	<0.01
The bronchial TB	7	14	37	26.8	<0.05
The bronchogenic rejection	17	34.0	100	74.6	<0.05
The hemoptysis	6	12.0	32	23.8	<0.05
The Respiratory failure	5	10.0	97	72.4	<0.001

Our studies show that the use of sputum PCR for the detection of MBT significantly increases the frequency of timely diagnosis of DR-PTB and the possibility of prescribing an optimal treatment regimen in 173 (94.0%) patients. Obstacles arise in the diagnosis of TB when patients have “small forms” of a specific process without destruction in the pulmonary parenchyma and are not bacteriostatic.

Researching of the resistance profile of MBT strains to AMBDs of the main group

When studying the resistance profile of MBT strains to AMBDs of the first line of the main group, it was found that resistance to HRES combinations was most often observed in 46.8% of DR-PTB, and in pre-XRPTB in 66.7%. Resistance to the combination of HRZ, HREZ, HR was the least common (Fig 1). In parallel, in pre-XRPTB, resistance to three or more AMBDs of the second line in combination with resistance to drugs of the first line prevailed (Fig 2).

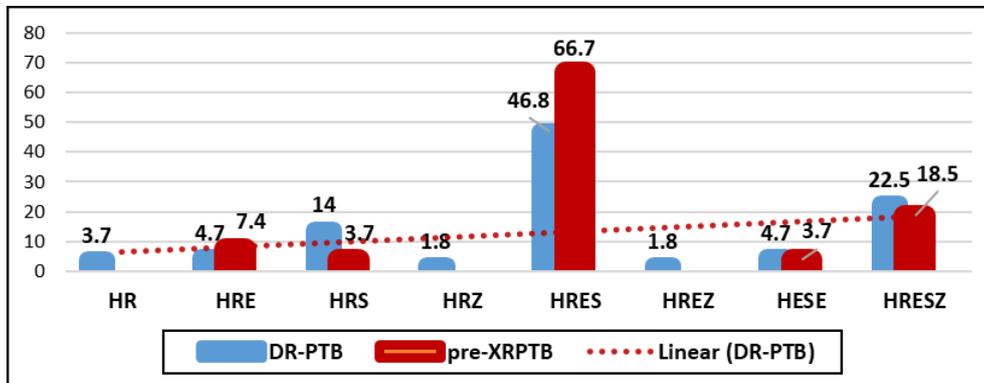


Figure 1: Frequency and profile of DR-PTB and pre-XDR-TB (%).

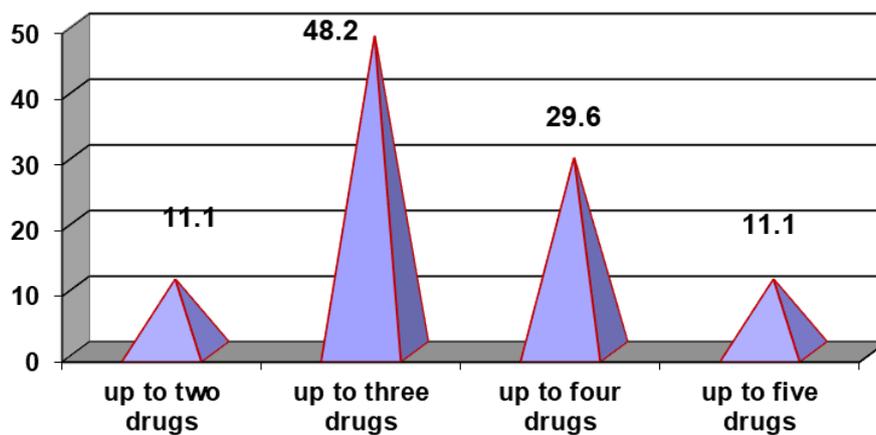


Figure 2: Frequency of resistance to first line drugs in pre-XDR-TB (%).

Therefore, microbiological examination methods, especially rapid molecular methods, for the detection of MBT in sputum and other pathological materials remain very important in the timely detection of patients who secrete bacteria and MBT strains sensitive/resistant to AMBDs.

In order to study the degree of biochemical disorders in patients with DR-PTB, the levels of: C-reactive protein (CRP), ceruloplasmin (CP) were studied. Determination of the level of these indicators was carried out in all examined patients. The normal limits of the indicators were determined when examining 21 healthy individuals, donors (Table 3). The level of CRP and CP in the blood serum was increased in almost all patients regardless of the sensitivity/resistance of the TB pathogen to AMBD. However, a significant increase in its level was more often determined in DR-TB, which indicated the presence of a pronounced inflammatory specific process.

Table 3: Frequency of changes in the intensity of the level of C-reactive protein in the examined groups of tuberculosis patients.

The indicators	The control group (n=50)		The main group (n=134)	
	abs.n.	%	abs.n.	%
up to 5 mg/l	3	6.0	5	3.8
6 - 20 mg/l	32	64.0	33	24.6
21- 30 mg/l	10	20.0	71	52.9
over 31 mg/l	5	10.0	25	18.8
Ceruloplasmin	40	80.0	129	96.3

Note: * The difference is significant compared to the control group (p<0.05).

Examinations of the functional state of the liver of TB patients revealed a slight increase in the activity of aminotransferases in the blood serum, the values of which were increased, compared to healthy ones, by an average of 1.3 - 1.4 times (Table 4).

Table 4: Changes in liver and kidney function indicators in patients with pulmonary tuberculosis.

The indicators	The healthy ones	The control group	The main group
		n = 50	n = 134
	(M ± m)	(M ± m)	(M ± m)
Thymol test (unit)	1.90 ± 0.17	1.86 ± 0.21	4.13 ± 0.15
Sulem sample (ml)	1.60 ± 0.22	1.92 ± 0.09	1.76 ± 0.13
Veltmann reaction (test tube)	6.0 ± 0.7	7.0 ± 0.3	8.5 ± 0.4
Total bilirubin level (µmol/L)	7.5 ± 0.6	8.9 ± 0.8	16.2 ± 0.4
ALT activity (mlmol/l)	0.31 ± 0.03	0.39 ± 0.02*	0.51 ± 0.05**
AST activity (mlmol/l)	0.42 ± 0.05	0.58 ± 0.04*	0.63 ± 0.03**
Urea (mmol/L)	4.3 ± 0.03	6.5 ± 0.02	7.5 ± 0.03
Creatinine (µmol/L)	79.3 ± 0.03	89.3 ± 1.05	93.3 ± 1.03

Notes: * The difference is significant compared to healthy individuals ($p < 0.05$); ** The difference is significant compared to the control group ($p < 0.05-0.01$).

The ALT values of the control and main groups corresponded to (0.39±0.02) mlmol/l and (0.51±0.05) mlmol/l, respectively, and (0.31±0.03) mlmol/l in healthy subjects ($p < 0.05$). The AST values were (0.58±0.04) mlmol/l and (0.63±0.03) mlmol/l vs. (0.42±0.05) mlmol/l in donors ($p < 0.05$).

Thus, in patients with TB before the start of AMBT, a slight increase (by 1.3–1.4 times) in transaminase activity was noted, with the preservation of normal osmotic-colloid properties of blood plasma (indicators of thymol, sulem tests, Weltman's reaction) and liver detoxification function (total bilirubin).

Immune status Research Laboratories

Determination of the phagocytic activity of the defense link in the formed groups showed that the total number of leukocytes in the blood of patients with DR-PTB was on average 1.3 times higher than in patients with S-PTB and amounted to (11.24±0.46) × 10³/µl (8.78±0.39) × 10³/µ, ($p < 0.05$) and (6.70±0.53) × 10³/µ, ($p < 0.01$) in donors (Table 5). Violations in the phagocytic chain of defense in the researched groups of patients differed not only in the intensity of changes, but also in their direction. Thus, in patients of the main group, inhibition of phagocytic activity of neutrophils was noted, while in the control group, phagocytosis was activated. In DR-PTB compared to S-PTB, the phagocytic index (PhI) decreased (by 1.3 times) to (64.6±2.4*)% relative to (79.9±1.2*)% ($p > 0.05$) and (67.1±3.1)% in donors, ($p > 0.05$, $p < 0.001$). Their absorption capacity (phagocytic number – PhN) decreased by 3.2 times to (5.6±0.3*■) relative to (14.1±0.4*), ($p < 0.01$) and (6.8±0.5) respectively, ($p < 0.01$). In addition, in patients of the main group (21.2±0.9*■), compared with the control one (18.6±0.7*), nitroblue tetrazolium reduction test (NTRT) was significantly increased, which, apparently, compensated for the insufficiency of cationic lysosomal proteins of granulocytes (CLPG) (75.5±1.1) vs. (59.8±1.5*■).

Table 5: Phagocytic defense indicators in patients with pulmonary tuberculosis caused by drug-sensitive and drug-resistant strains of MBT.

The indicators	The groups		
	The donor (n= 30)	The control (n=22)	The main (n= 25)
	(M±m)	(M±m)	(M±m)
Total leukocytes	6.70±0.53	8.78±0.39*	11.24±0.46*■
PhN (%)	6.8±0.5	14.1±0.4*	5.6±0.3*■
PhI (%)	67.1±3.1	79.9±1.2*	64.6±2.4■
NTRT (%)	9.3±0.8	18.6±0.7*	21.2±0.9*■
CLPG (%)	78.6±2.4	75.5±1.1	59.8±1.5*■

Notes: * The difference is significant relative to the donor group ($p < 0.05-0.01$); ■ The difference is significant relative to the reference group ($p < 0.05-0.01$).

Table 6: Population composition of lymphocytic blood cells in patients with pulmonary tuberculosis depending on the sensitivity/resistance of MBT strains in adults.

The indicators	The groups		
	The healthy ones (n=15)	The control (n=23)	The main (n=25)
CD3+ T-lymphocytes (%)	71.5±2.5	73.4±2.2*	51.2±3.1*
T-helper lymphocytes CD3+CD4+ (%)	41.0±2.7	33.8±2.1*	30.4±1.8*
T-suppressor/cytotoxic CD3+CD8+ (%)	28.5±1.4	29.4±1.7	36.3±1.5*,#
Ratio CD3+CD4+/ CD3+CD8+ (IRI Tx/Tc)	1.30±0.08	1.15±0.06	0.84±0.07*,#

Notes: * Significant difference compared to donors ($p < 0.05$); # Significant difference compared to control group ($p < 0.05$).

In patients with PTB, regardless of the type of sensitivity/resistance of the pathogen, a decrease in the total number of T-lymphocytes was noted. The population of T-lymphocytes with expression of the CD3+ antigen in the examined patients of both groups was (63.4±2.2)% and (61.2±3.1)% compared to (71.5±2.5)% in healthy subjects ($p < 0.05$). In adult patients with S-PTB and DR-PTB, a significant increase in pro-inflammatory interleukins was noted in the blood. In DR-PTB and relative to S-PTB, TNF- α increased by 2.7 times (55.5 pg/ml vs. 20.7 pg/ml, $p_1 < 0.05$), and relative to donors this indicator increased by 37.7 and 14.1 times ($p_2 < 0.01-0.001$). Similar changes were noted at IL-6 increased by 1.9 times ($p_1 < 0.05$), and relative to donors by 1.9 and (29.6±4.40 vs. 15.2±2.09, $p < 0.05$) and by 17.2 times relative to the indicators of the main group with donors (29.6±4.40 vs. 1.72±0.14), ($p_2 < 0.05-0.001$), (Table 7).

Table 7: Serum cytokine levels in patients with S-PTB and DR-PTB.

The indicators	The researched groups		
	The donor (n=17)	The control (n=25)	The main (n=20)
TNF- α pg/ml	1.47±0.12	20.7±3.09*,**	55.5±3.72*,**
IL-6 pg/ml	1.72±0.14	15.2±2.09*,**	29.6±4.40*,**
IL-10 pg/ml	5.14±0.26	3.9±0.61	5.5±1.01
IL-6/IL-10	0.33±0.07	5.1±0.43*,**	6.3±0.83*,**

Notes: * The difference is significant in relation to the main group to the control one ($p_1 < 0.01-0.001$). ** The difference is significant in relation to the examined groups to the donors ($p_2 < 0.05-0.001$).

The production and release of pro-inflammatory cytokines TNF- α , IL-6 were found to be significantly more frequent in patients of the main group. In patients with DR-PTB, a tendency to increase IL-6/IL-10 was found 1.4 times compared to the control group ($p_1 > 0.05$) and a tendency to decrease its level, respectively, in donors ($p_2 > 0.05$).

According to the WHO, antibiotic resistance is one of the most serious threats to human health today. The increasing prevalence of antibiotic resistance is reducing the effectiveness of healthcare delivery worldwide, requiring a comprehensive approach. The consequences of pathogen resistance include increased medical costs, longer hospital stays and increased mortality. The problem of untimely diagnosis of TB and differential diagnosis of the tuberculosis process in the lungs with community-acquired pneumonia is acute [11]. Anti-tuberculous drugs remain one of the most effective methods for combating life-threatening bacterial infectious diseases. However, the success of treatment depends on the justified appointment of treatment, the timeliness of use and the correct choice of AMBDs.

In our study, it was found that disseminated TB was diagnosed 1.5 times more often and fibro-cavernous TB 1.7 times more often ($p < 0.05$) in patients with DR-PTB. In addition, the progression of the specific process was 3.7 times more often manifested by caseous pneumonia ($p < 0.01$), bronchogenic rejection 2.2 times and bronchial TB 1.9 times ($p < 0.05$). An increase in ESR above 31 mm/h was detected in 23.8% of the examined of the main group, which is significantly more frequent than in control (7; 14.0%). Resistance to HRES combinations in DR-PTB was found in 46.8% of patients. High levels of CRP and CP were found 70.9% of cases with DR-PTB. In 71.7% of patients with PTB a 1.3–1.4-fold increase in transaminase activity was noted, with the preservation of normal osmotic-colloid properties of blood plasma and detoxification function of the liver before the start of AMBT. DR-PTB is characterized by a more pronounced suppressive nature of the cellular response, as well as a probable increase in pro-inflammatory interleukins in the blood.

Conclusion

The clinical and radiological course of a specific process depends on the sensitivity/resistance of MBT. The researches indicate the importance of multimodal clinical and laboratory diagnostics of DR-PTB, which in the future will help in the timely initiation of treatment and selection of appropriate therapy regimens, as well as control of the spread of drug-resistant tuberculosis.

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