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NIKOLAEV ALEXEY VLADIMIROVICH

IMMUNE AND ENDOCRINE MECHANISTIC LINKS OF TUBERCULOSIS AND PULMONARY SARCOIDOSIS: CLINICAL AND PATHOPHYSIOLOGICAL CHARACTERISTICS

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Scientific supervisor:
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associate professor
Churilov Leonid Pavlovich

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CONTENT

LIST OF ABBREVIATIONS

AAT - autoantibodies

ACE - antiotensin-converting enzyme AT antibodies

AM - alveolar macrophages

AOP - antioxidant protection

AOS - antioxidant system

APC - antigen presenting cells

BAL - bronchoalveolar lavage

BAS - biologically active substances

BMD - bone mineral density

cAMP - cyclic adenosine monophosphate

cGMP - cyclic guanosine monophosphate

CIC - circulating immune complexes

CKL - chemokine ligands

CRP – C-reactive protein

CT - computed tomography

DC - dendritic cells

DIL - diffuse interstitial and disseminated lung diseases

DPL - disseminated pathology of the lungs

DTH - delayed-type hypersensitivity

EI - endogenous intoxication

ELI test - translation of ELI - enzyme ligated immunoassay

FEV - forced expiratory volume

FI - phagocytic index

FN - fibronectin

FVC - forced vital capacity

GIT - gastrointestinal tract

HMH - human major histocompatibility complex Ig - immunoglobulin

HRCT - high-resolution computed tomography

IFN - interferon

IL - interleukin

IS - secretion index

ITLN - intrathoracic lymph nodes

LII - leukocyte index of intoxication

LPO - lipid peroxidation

MBT - Mycobacterium tuberculosis

MDR - multidrug resistance

MlCT - multilayer computed tomography

MODS - syndrome of multiple organ failure (failure)

MRI - magnetic resonance imaging

NADH - nicotinamide adenine dinucleotide

NII - nuclear index of intoxication

NO - nitric oxide

NST-test - test with nitrosine tetrazolium

OND - organs of natural detoxification

PCR - polymerase chain reaction

PET - Positron Emission Tomography

PR - pregnant-X receptor

PTH - parathyrin, parathyroid hormone

RF - Russian Federation

ROS - reactive oxygen species

RP - radiopharmaceutical

SL - sarcoidosis of the lungs

SPECT - single photon emission computed tomography

TL - pulmonary tuberculosis

TNF - tumor necrosis factor

TSH - thyroid stimulating hormone

VC - vital capacity of the lungs

VDR - vitamin D receptor

WHO - World Health Organization

INTRODUCTION

Relevance of the topic

The share of diffuse interstitial and disseminated lung diseases (DLD) accounts for about 5% of all pulmonary pathology and in recent decades there has been an increase in their occurrence [Nikolaev A.V. et al. 2021, Yablonsky P.K., 2016; Nikitin V.A. et al., 2018; Morris Timothy A. et al., 2014; Pokorski M., 2018].

According to the literature, 50-70% of patients with DLD are initially misdiagnosed as "pulmonary tuberculosis" (PT) with unjustified chemotherapy, which leads to chronicity of the pathology with the appearance of frequent relapses and, accordingly, to an increase in disability and mortality of patients [Drobot N.N. , 2017; Nikolaev A.V. et al. 2021, Matsuyama T. et al., 2011]. At the end of the last century, some scientists believed that tuberculosis was a “disappearing disease”, but this turned out to be deeply erroneous not only for Russia, but for the world as a whole: at present, according to experts from the World Health Organization (WHO), about 9 million people, about 5 thousand people die per day [Nikolaev A.V. et al. 2021, Carrillo-Perez D.L. et al., 2015].

In the Russian Federation (RF), the situation with tuberculosis is “unsustainable” and against the background of a slight decrease in the overall incidence, there is the formation of many drug-resistant (MDR) forms of Mycobacterium tuberculosis (MBT) [Ashenova G.Zh. et al., 2018; Sterlikov S.A. et al., 2018].

In the world in 2016, 490,000 new cases of PT with MDR MBT were registered, effective treatment with traditional drugs in such patients is noted only in 26% of cases, due to the development of chemotherapy complications (toxic damage to the ears, liver, kidneys, etc.), which cause patients are no longer treated, the same is true for the price: a course of therapy for such patients costs 440,000 rubles. [Nikolaev A.V. et al. 2021, Pavlova M.V. et al., 2015; Kulish Skak et al., 2016; Kildyusheva E.I. et al., 2017; Lapshina S.M. et al., 2018]. Accordingly, for

many reasons, forecasts regarding TH in the world are pessimistic [Dheda K.A. et. al., 2010], and in 2022, for the first time since 1997, a WHO report noted a global increase in the incidence of tuberculosis [Dean AS et al (2022)].

Pulmonary sarcoidosis (PS) also belongs to DLD [Nikolaev A., Churilov L. 2012]. In relation to all patients with active PT, patients with SL account for 5.0%, but in recent years there has been a significant increase in the incidence due to previously unverified cases, due to the improvement of diagnostic methods and a true increase in the incidence of sarcoidosis, which in all countries after the introduction of anti-tuberculosis vaccination had a cross dynamics in relation to tuberculosis [Ariel B. M., 2005; Jassal M.S., Bishai W.R., 2010].

Patients with PS are people of working age (20-50 years), however, there are separate reports of the detection of this form of pathology in preschool children, adolescents and the elderly, while an adequate approach to identifying and treating the disease contributes to a good prognosis, recovery of health and working capacity [Brazhenko N.A., 2015; Zaitsev A. A. et al., 2015; Shanthikumar S., Harrison J., 2015].

The prevalence of PS in the world ranges from 1 to 40 per 100,000 population, and the incidence increases by about 2% per year [Adrianto I. et al., 2012; Kumar R. et al., 2012; Babu K., 2013]. Previously, in the USSR, the SL problem was assessed only on the basis of statistics from tuberculosis dispensaries where patients were observed [Terpigorev, S. A., 2013; Gavrisyuk V.K. et al., 2014; Vizel A.A. et al., 2017]. Currently, patients with SL are under the supervision of general practitioners, they the diagnosis of the disease is often associated with significant difficulties [Antipushina D.N., Zaitsev A.A., 2015; Koth L.L. et al., 2011].

There is still no clarity on the causes of the development of PS, but the existing hypotheses of the so-called "infectious etiology" refer to triggers of mycobacteria (classic and filterable forms), viruses of the herpes group, etc .; and "environmental factors" - adjuvants include microbial agents and chemical components - smoke, silicone, dyes, etc.) and, according to this theory, exogenous

anthropogenic and natural factors in individuals with a genetic predisposition cause a direct toxic effect on the cells of the human body [Nikolaev A.V. et al. 2021].

When reactive compounds are formed that interact with cell membranes, nucleic acids, proteins with the formation of neoantigens, membrane toxins and even carcinogens (mutagens), trigger and adjuvant effects appear on the cells, which activates the mediator systems of inflammation, causes allergoic reactions, leading to the production of biologically active signaling molecules of short-range and focal action ("autacoids") [Nikolaev A.V. et al. 2021, Churilov L.P., 2021; Connor M.R., Stevens R.S., 2012].

Since the 1970s, many researchers have tried to prove the clinical and pathophysiological commonality of PT and PS [Ilkovich M.M. et al., 2014; Belokurov M.A. et al., 2018; Chen E.S., Moller D.R., 2015]. In a number of patients with sarcoidosis, components of mycobacteria and antibodies to them were found, which was the reason for the appointment of anti-tuberculosis therapy [Scadding J.G., 1960; Moscovic E.A., 1978; Khomenko A.G. et al., 1996].

The role of MBT as the main etiological factor of sarcoidosis has not been confirmed, but the concept of tuberculosis and sarcoidosis as two variants of the response of the body's reactivity to close or even identical etiological factors (perhaps on a different mosaic-permissive background) is not rejected and finds supporters [Nikolaev A.V. et al. 2021, Hurster R. Et. Al., 2009; Gupta D. et. al., 2012; Agrawal R. et. al., 2016].

The degree of development of the research topic

In general, literature data indicate that at present the problem of etiopathogenetic differences between PT and PS has not been resolved and today there are several trends:

• increase in morbidity and mortality in granulomatous pulmonary pathology;

• limitation of the possibilities and resolution of the methods of complex diagnostics of SL due to the ambiguity of its etiology; an increase and some reassessment of the role of visual methods of radiation diagnostics (X-ray, CT, etc.);

• disunity of data on hematological, immune, hormonal, toxicological, vitaminological aspects of the pathogenesis of PS narrows the possibilities of using these data for differential diagnosis, and, therefore, for early prevention and treatment of this form of pathology;

• the emergence of new methods of laboratory diagnostics, for example, assessment of the spectrum and intensity of autoimmunity in non-competitive enzyme-linked immunosorbent assay with panels of marker autoantigens (ELI-test) [Poletaev A.B., 2010; Babanov S.A., 2013; Mezhebovsky V.R. et al., 2014; Starevskaya S.V. et al., 2015; Bettoncelli G., 2014; Jin X. et al., 2015; Mirsaeidi M. et al., 2015].

The purpose of the study

was to compare the clinical and pathophysiological characteristics of PT and PS and to identify the pathophysiological prerequisites for new differential diagnostic signs of these diseases.

Research objectives

1. To compare clinical features in patients with verified PT or PS, as well as endocrine-metabolic and immunological parameters that characterize pathogenesis.

2. To study the spectrum and intensity of autoimmunity in PT and PS.

3. To study the diagnostic significance of the results of modern instrumental methods for assessing the function of external respiration in tuberculosis and sarcoidosis of the lungs.

4. Assess the diagnostic capabilities of radiography and computed tomography of the lungs in tuberculosis and sarcoidosis of the lungs.

5. To clarify the optimal criteria for a pathophysiologically substantiated differential diagnosis of tuberculosis and pulmonary sarcoidosis to improve the quality of treatment and preventive care for these patients.

Scientific novelty

It has been established that in patients in a compensated state with PT and PS (to a lesser extent) there is an ISDA-syndrome (in the classical literature called "endogenous intoxication"). At the same time, against the background of vitamin D deficiency, accumulation in patients of pro-inflammatory cytokines (autacoids), procalcitonin (with PS, we documented its increase in the blood of patients for the first time in the world literature) and the development of a protective inflammatory response of the body in the form of a reaction from clinical blood (anemia, leukocytosis , increased erythrocyte sedimentation rate (ESR)), tension of the function of natural detoxification organs (NDO; liver, kidneys, lungs) and regulatory systems (hypercorticism, euthyroidism, increased levels of pituitary hormones - thyroid-stimulating hormone (TSH) and lactogen). At the same time, an increase in the blood levels of the active form of vitamin D (to a greater extent in PS), the antimicrobial peptide LL-37 cathelicidin (to a greater extent in PT), activation of innate immunity, cellular (adaptive), humoral immunity and autoimmunity were found. Autoimmune manifestations in granulomatous diseases were confirmed in the ELI-test, they were mosaic and multi-organ in nature: in the group of patients with PT among 24 tests, the values of the studied parameters with the “+” sign were in 10 samples (for lung antigens LuS-06 LuM-02 were with the sign (-), and in PS - in 15 samples, including lung antigens LuS-06 LuM-02. In general, the results of the ELI-test indicated that, having a similar pathomorphological basis, this granulomatosis differ in pathogenesis and

involvement of different organs and systems in the immunopathological process [Nikolaev A.V. et al. 2021].

Functional tests and radiation diagnostic methods confirmed the presence of morphological substrates for the development of ISDA in PT (mainly restrictive and mixed dysfunctions in fibrosis and large foci-infiltrates of the lung tissue) and TS (mainly obstructive and mixed dysfunctions in mediastinal lymphadenopathy and many tiny foci of tissue damage lungs.

The theoretical significance of the work

It has been shown that in PT and PS of different etiologies, there are unidirectional similar manifestations of the immunopathogenesis of diseases with excessive systemic action of pro-inflammatory autacoids (ISDA), which is more pronounced in PT, and immune inflammation is accompanied by distinct manifestations of autoreactivity, which is more pronounced in PS, including in in relation to lung tissue [Nikolaev A.V. et al. 2021]. It was not found in LT, possibly due to rational treatment and compensatory immunometabolic changes with an increase in cortisol and prolactin levels. At the same time, a significant dependence of the manifestations of autoimmunity on vitamin D deficiency and the characteristics of the metabolism of its active form, calcitriol (more elevated in PS), as well as the antimicrobial peptide cathelicidin, the expression of which is vitamin D-dependent (more elevated in PT), was revealed.

The main target in PT is the lung tissue, while in PS it is the airways, which was confirmed by the results of instrumental methods for studying the function of external respiration (in PT - predominantly restrictive-mixed disorders, in PS - predominantly obstructive-mixed disorders) and radiation diagnostic methods.

The practical significance

For the first time, the importance of complex laboratory, instrumental and radiological diagnostic methods for assessing the condition of patients with tuberculosis and sarcoidosis of the lungs is shown. An algorithm of actions for a practitioner is proposed in the form of an analysis of complaints, clinical data, the results of clinical, laboratory, and instrumental studies, including immunograms, cytokine, hormonal, and vitamin-D status, an assessment of the function of external respiration, and the results of radiation methods.

Methodology and research methods

The study used a methodology that takes into account modern standards when conducting examinations of patients with tuberculosis and sarcoidosis of the lungs. The study of homeostasis indicators in patients was carried out using complex informative immunological and biochemical clinical and laboratory, clinical and pathophysiological instrumental tests, as well as radiological methods, carried out in dynamics, the quantitative results of which were subjected to adequate computer statistical processing.

The main provisions for defense

1. In PT and PS (to a lesser extent) there is an ISDA-syndrome due to the accumulation of autacoids in the systemic circulation, which is manifested by a tendency to anemia, inflammatory changes in the clinical blood test, an increase in the leukocyte index of intoxication according to Kostyucheno-Sokolov, a Dashtayants's nuclear index of intoxication , a shift in biochemical analyzes towards the border "normal-pathology", an increase in plasma levels of cortisol, procalcitonin, prolactin and TSH.

2. In PT and PS (to a lesser extent), protective activation of nonspecific paleoimmunity (an increase in the levels of the spontaneous and stimulated NBT-test with a decrease in the reserve capacity of granulocytes to digest pathogens), activation of cellular immunity (an increase in the average levels of the total number of lymphocytes, T-, B -lymphocytes, natural killers with a decrease in T-helpers, the ratio of CD4+/CD8+), activation of humoral immunity. The identified hypovitaminosis D was compensated by elevated levels of its activated form (calcitriol, mostly in TS), and vitamin D-associated antimicrobial protein cathelicidin (to a greater extent in PT).

3. In the ELI-test in PT and PS (to a greater extent), data characteristic of the activation of autoimmunity were noted: elevated levels of AAB to autoantigens of various organs and systems (with PT in 10 out of 24 samples, with PS - 15 out of 24 samples, but in relation to lung tissue antigens, elevated levels of AAB were only in sarcoidosis, and were below normal in PT).

4. In PT, the parenchyma of the lungs is predominantly affected, and restrictive-mixed forms of violation of the ventilation function of the lungs predominate. In PS, the bronchopulmonary region is predominantly affected, and obstructive-mixed pulmonary dysfunctions predominate.

5. Computed tomography, in comparison with radiography of the lungs, is more informative than radiography of the lungs; for PT, the characters are single large foci, bronchiectasis and pleural effusion, and for PS, mediastinal lymphadenopathy, small-focal dissemination, massive fibrosis and calcifications in the structure of the lymph nodes.

The degree of reliability and approbation of the work

The reliability of the study results is based on sufficient clinical material: 125 patients with PT (53), with PS (42), practically healthy people (30), given the homogeneity of the composition of each of the compared groups, with adequate

methods of computer statistical processing of quantitative clinical and laboratory data instrumental-beam studies.

The main results of the study were reported and discussed at international and all-Russian and with international participation scientific and practical conferences (see below the list of published works).

Implementation of research results into practice

The data obtained as a result of the study were introduced into the medical and diagnostic work of the Department of Radiation Diagnostics of the Military Medical Academy, are used at St. autoimmunology (5th year students).

Publications on the research theme

On the topic of the dissertation, 12 publications were published, 4 of them in peer-reviewed scientific journals recommended by the Higher Attestation Commission of the Ministry of Education of the Russian Federation for publication of the main results of dissertations for the PhD.

Applicant's personal contribution.

The author independently developed the design and program of the study, and took part in the examination and management of patients with sarcoidosis and pulmonary tuberculosis; mastered the methods of diagnosing pathology, performed a statistical analysis of quantitative indicators. The author independently selected and analyzed the literature, carried out a description of the results of clinical, laboratory, instrumental and radiation methods of research, formulated conclusions and main provisions submitted for defense.

The volume and structure of the dissertation.

The dissertation is presented on 187 pages of typewritten text and consists of an introduction, literature review, description of materials and research methods, two chapters of the results of own research, conclusions, conclusions, practical recommendations, includes 23 tables and 21 figures. The list of references contains 412 bibliographic sources, including 124 in Russian and 288 in foreign languages.

CHAPTER 1 CLINICAL AND PATHOPHYSIOLOGICAL BASES OF DIFFERENTIAL DIAGNOSIS OF TUBERCULOSIS AND PULMONARY SARCOIDOSIS

1.1 Etiology and epidemiology of tuberculosis and pulmonary sarcoidosis

The share of diffuse interstitial and disseminated lung diseases (DLD) accounts for about 5% of all pulmonary pathology [Nikolaev A.V. et al. 2021, Yablonsky P.K., 2016; Nikitin V.A. et al., 2018; Morris T. et al., 2014; Pokorski M., 2018]. According to the literature, 50-70% of patients with DLD, including those with pulmonary sarcoidosis (PS), are initially diagnosed with pulmonary tuberculosis (PT) with unreasonable anti-tuberculosis chemotherapy, which leads to adverse consequences, including disability and mortality of patients [Nikolaev A.V. et al. 2021, Drobot N.N., 2017; Matsuyama T. et al., 2011].

1.1.1 Pulmonary tuberculosis

In the last quarter of the last century, some experts considered tuberculosis a “disappearing disease”, but this turned out to be deeply erroneous not only for Russia, but for the whole world. In 1993, the World Health Organization (WHO) declared the “rebirth” of this disease an extraordinary event in the world and noted that in 2015, 10.4 million people fell ill with tuberculosis, incl. 5.9 million (56.0%) men, 3.5 million (34.0%) women, 1.0 million (10.0%) children. At the same time, 60.0% of cases were in six countries: India, Indonesia, China, Nigeria, Pakistan and the Republic of South Africa. In 2017, 1.7 million people died from tuberculosis in the world, and tuberculosis infection remains one of the 10 leading causes of death in people, ahead of HIV and malaria in importance [Nikolaev A.V. et al. 2021, Carrillo-Perez D.L. et al., 2015; Matteelli A. et al., 2016; World Health

Organization, 2016, 2017, 2018].PT is an infectious disease and its causative agent M. tuberculosis was discovered by R. Koch in 1882. Today it is known that this disease can be caused by mycobacteria (MBT): M. tuberculosis, M. bovis, M. africanum, and it has been proven that the main route of infection transmission (up to 95%) is airborne [Nikolaev A.V. et al. 2021, Tolstykh A. S., Shugaeva S. N., 2015; Davies Peter D.O., 2016].

R. Koch himself called ST "tears of poverty", since the incidence of the population directly depends on the standard of living. In economically developed countries, including the USSR, in the second half of the last century, the main epidemiological indicators stabilized at a low level, which supported optimism regarding the “elimination of tuberculosis” as a mass disease [Nikolaev A.V. et al. 2021, Perelman M. I., Bogadelnikova I. V., 2015; Rios M., Monleon-Getino T., 2009].

More often, ST affects men (69-75%), but in recent years there have been reports of an increase in the incidence in children and pregnant women [Aksenova V.A. et al., 2015; Valeeva G.A., 2015; Nikolaev A.V. et al. 2021, Pavlunin A. V., 2018; Starke J.R., Donald P.R., 2016].

In Russia and in the republics of the former USSR, after many years of stabilization, in the 90s. In the 20th century, due to the socio-economic crisis, the incidence of PT increased, but from 2008 to 2017 in the Russian Federation, the indicator decreased from 85.1 to 48.3 per 100,000 population (by 43.2%); in children 0–14 years old - from 15.3 to 9.7 per 100,000 children (by 36.6%) [Vasilyeva I.A. et al., 2017; Kandrychyn S.V., 2017; Nechaeva O.B., 2018; Nikolaev A.V. et al. 2021, Federal State Statistics Service, 2018].

There is an opinion that overdiagnosis of PT is possible due to an increase in the number of cases of mycobacteriosis caused by non-tuberculous mycobacteria [Nikolaev A.V. et al. 2021, Ergeshov A.E. et al., 2016].

After the isolation of a group of proteins expressed during MBT reproduction, called ESAT-6 and CFP-10, new in vitro immunological diagnostic tests were created (IGRA-tests: QuantiFERON (QFT)-TB, T-SPOT.TB test, IP-

10) and in vivo (with tuberculin, with recombinant tuberculosis allergen; test with Diaskintest) [Nikolaev A.V. et al. 2021, Kislichkin N.N. et al., 2016]. Diaskintest was developed in Russia, it also uses non-sensitizing and non-toxic proteins ESAT-6 and CFP-10, which are absent in M. bovis from BCG strains, as an allergen, which makes it possible to distinguish post-vaccination allergy from infectious [Litvinov V. I., 2009; Nikolaev A.V. et al. 2021, Zinchenko Yu.S. et al., 2018].

However, the use of these tests does not allow differential diagnosis between latent tuberculosis infection (LTBI) and active tuberculosis (AT). In the presence of characteristic radiological changes, bacteriological verification of the diagnosis of AT was obtained only in 46% of cases, and the determination of specific immune complexes (IC) by dynamic light scattering after the addition of antigens of specific peptides ESAT-6 and SFP-10 in vitro made it possible to determine AT in 100% of cases. and identify a high-risk group for its development in individuals with LTBI [Nikolaev A.V. et al. 2021, Starshinova A.A. et al., 2019]. These data indicate that the etiological factor does not exhaust the entire etiology of tuberculosis and its course depends on the body's response to MBT, which, to the extent of the reactivity of individuals, primarily immunological, can be very different [Nikolaev A.V. et al. 2021, Dheda K. et al. 2010].

Currently, with PT, there is a formation of a severe clinical structure in the form of destructive and bacillary tuberculosis, its combination with HIV infection, the formation of multidrug-resistant (MDR) forms of MBT [Ashenova G.Zh. et al., 2018; Nikolaev A.V., 2020, Sterlikov S.A. et al., 2018]. According to WHO, in 2016, 490,000 new cases of TB with MDR MBT were registered in the world, and effective treatment in such patients is noted only in 26% of cases, complications of chemotherapy (toxic damage to the hearing organs, etc.) force doctors and patients to refuse continuation of treatment [Lapshina S.M. et al., 2018 Nikolaev A.V. et al. 2021]. When using new drugs, the cost of treating a patient with PT with MDR MBT reaches 440,000 rubles, which is 160 times higher than when using conventional drugs (2745 rubles) [Nikolaev A.V. et al.

2021, Pavlova M.V. et al., 2015; Kulish Skak et al., 2016; Kildyusheva E.I. et al., 2017].

With incurable PT in combination with concomitant diseases (liver, kidneys, etc.), leading to mortality, so-called "palliative care" programs are being developed for patients [Balasanyants G.S. et al., 2014; Kolpakova T.A., 2016; Mokhryakova T.E., Sinitsyn M.V., 2016; Borodulina E. A. et al., 2017; Nikolaev A.V. et al. 2021, Burnasheva L.S. et al., 2017; Plotnikov V.P. and others, 2019; Connor S., Cepulveda C., 2014].

WHO specialists call for the next “elimination” of PT by 2030, but it is very difficult to imagine, since the incidence of PT population depends on many conditions: genetic, regional characteristics (demographic, social, economic, standard of living and education, intensity and directions of migration etc.); from political and economic factors (crises, conflicts); on the prevalence of tuberculosis in the penitentiary system; on the effectiveness of anti-tuberculosis measures (organization of prevention, timely detection, quality of work of laboratory and radiological services, etc.) [Zorkaltseva E. Yu. et al., 2016; Bagirov M.A. et al., 2018; Ivanova D.A. et al., 2018; Hatfull G.F., Jacobs W.R., 2014; Cantey J. B. et. al., 2018; Tamanna T. et. Al., 2018]. There are also pessimistic forecasts due to growing poverty, the spread of HIV and MDR in a number of regions of the world [Dheda K.A. et. al., 2010]. Thus, the presented literature data indicate that the problem of PT has not disappeared and even acquired a new relevance.

1.1.2 Sarcoidosis of the lungs

Sarcoidosis is a polysystemic disease of unknown etiology, with a heterogeneous clinical course characterized by the formation of noncaseating epithelioid cell granulomas, the accumulation of CD4+ T-lymphocytes in the foci of productive inflammation in a Th1/Th17-dependent immune response. [Ershov G.A., Churilov L.P., 2017]. These granulomas are the pathomorphological substrate of the disease formed as a result of delayed-type hypersensitivity, and

the processes of transformation, recruitment and final differentiation of cells in these granulomas are regulated by cytokines and chemokines - peptides of communication of the immune system [Nikolaev A.V. et al. 2021, Chuchalin A.G. et al., 2014, Churilov L.P., 2021].

These granulomas are the pathomorphological substrate of the disease formed as a result of delayed-type hypersensitivity, and the processes of transformation, recruitment and final differentiation of cells in these granulomas are regulated by cytokines and chemokines - peptides of communication of the immune system [Nikolaev A.V. et al. 2021, Chuchalin A.G. et al., 2014, Churilov L.P., 2021].

In recent years, there has been a significant increase in the incidence of PS, which is associated both with an improvement in diagnosis and a true increase in the incidence of this form of pathology, which in all countries after the introduction of tuberculosis vaccination had a reciprocal dynamics in relation to tuberculosis infection [Ariel B. M., 2005 ; Jassal M.S., Bishai W.R., 2010].

As a rule, the contingent of PS patients is people 20-50 years old, although the disease can affect preschool children, adolescents and the elderly [Brazhenko N.A., 2015; Zaitsev A. A. et al., 2015; Starevskaya S.V. et al., 2015; Nathan N. et al., 2015; Ramanantsoa A., et al., 2015; Shanthikumar S., Harrison J., 2015].

In relation to all patients with active LT, patients with SL make up 5.0%, the average prevalence of the disease in the world is 20 cases per 100,000 population, and its incidence increases by about 2% per year [Jassal M.S., Bishai W.R., 2010] .

At the same time, the prevalence of sarcoidosis per 100 thousand of the population among African Americans is 2-7 times higher than among US citizens of other ethnic origin, and is more than 100 cases, in the Scandinavian countries - 40-70, in the countries of the Southern Hemisphere it occurs much less frequently, than in the countries of the Northern Hemisphere, which is associated not only with regional natural features, but also with the absence or low intensity of the implementation of disease detection programs [Nikolaev A.V. et al. 2021,

Adrianto I. et al., 2012; Kumar R. et al., 2012; Maertzdorf J. et al., 2012; Babu K., 2013; Brito-Zerun P. et al., 2018].

In Russia, the incidence of PS until 2003 was in the range of 2 to 7 people per 100,000 adults [Nikolaev A.V. et al. 2021, Terpigorev, S. A., 2013; Fleming M.F. et al., 2006]. In Kazan in 2002, the first active screening of patients with pulmonary sarcoidosis was carried out: the prevalence was 64.4 per 100 thousand, cases of familial sarcoidosis occurred in 3%, while in the UK this figure was 1.7%, in Ireland - 9 .6%, in Finland - 3.6% in Japan - 4.3%. In general, the prevalence of SL in Russia has regional variations from 22 to 47 per 100 thousand of the adult population [Nikolaev A.V. et al. 2021, Chuchalin A.G. et al., 2014].

Women with PS have more pronounced clinical manifestations of the disease than men, which is also characteristic of other diseases of autoimmune origin [Nikolaev A.V. et al. 2021, Churilov L.P., 2021; Louzir B. et al., 2011; Shoenfeld Y. et al., 2011]. Mortality from sarcoidosis in Russia and abroad ranges from 0.3% to 7.4%, and the consequences of concomitant cardiac, respiratory, renal failure, and oncopathology are common causes of death [Gavrisyuk V.K. et al., 2014; Mezhebovsky V.R. et al., 2014; Nikolaev A.V. et al. 2021, Vizel A.A. et al., 2017; Mirsaeidi M. et al., 2015; Els Beijer et al., 2017]. It is also possible the death of patients against the background of the applied immunosuppressive therapy and from the accession (or activation of a latent) infection (PT, HIV, leprosy) [Gumenyuk G.L. 2015; Nikolaev A.V. et al. 2021, Al-Khouzaie T.H. et al., 2011; Dziadzio M. et al., 2011; Duncan M.E., Goldacre M.J., 2012; Maertzdorf J. et al., 2012; Scheibe F. et al., 2012; Dubaniewicz A. et al., 2013; Sadek M.M. et al., 2014; Spagnolo P. et al., 2018].

Despite the established nosological features of this form of pathology, there is still no clarity on the etiology of PS, although, nevertheless, there are several hypotheses.

The hypothesis of infectious etiology is confirmed in the experiment by the possibility of transmission of PS from animal to animal, as well as during transplantation of donor organs to humans [Nikolaev A.V. et al. 2021, Oswald-

Richter K.A., Drake W.P., 2010]. Infectious factors are considered as triggers: constant antigenic stimulation contributes to the dysregulation of cytokine production in individuals genetically predisposed to such reactions, which can trigger autoinflammatory and autoimmune processes [Nikolaev A.V., 2020, Chakravarty S.D. et. al., 2012]. The most common triggers for PS include mycobacteria (classic and filterable forms) and Propionibacterium acnes. Less often describe data in favor of the role of Chlamydophila pneumoniae; Borrelia burgdorferi; mold fungi; individual viruses, in particular, hepatitis C, herpes group, JC virus [Babanov S.A., 2013; Nikolaev A.V. et al. 2020, Tercelj M. et al., 2011; Saidha S. et al., 2012; Bandyopadhyay D. et al., 2014; Carrillo-Perez D.L. et al., 2015; Celada L.J. et al., 2015].

The hypothesis of the influence of "environmental factors" comes from the fact that not only microbial agents, but also smoke, toner powder of printers and copiers, components of implanted silicone prostheses, have antigenic and / or adjuvant properties and the ability to stimulate the formation of tuberculous granulomas in the lungs, tattoo pigments, asbestos, some dyes, agricultural, road and metal dust containing adjuvant or hapten metals: compounds of aluminum, barium, beryllium, cobalt, copper, mercury, gold, rare earth metals (lanthanides), titanium, zirconium. Studies of specialists involved in the ACCESS program (A Case-Control Etiology Study of Sarcoidosis) and other scientists have shown an increased risk of developing professional PS in builders, gardeners, teachers, firefighters, military personnel, etc. [Antipushina D.N., Zaitsev A.A. ., 2015; Nikolaev A.V., 2020, Oswald-Richter K.A., Drake W.P., 2010; Al-Khouzaie T.H. et al., 2011; Morgenthau A.S., Iannuzzi M.C., 2011; Tchernev G. et al., 2012; Sun H.H. et al., 2013; Bettoncelli G., 2014].

Hypotheses about the role of exogenous anthropogenic and natural factors in the etiology of sarcoidosis do not contradict the ideas about its autoimmune and/or autoinflammatory pathogenesis that have been actively developing in recent years [Nikolaev A.V. et al. 2020, Starshinova A.A. et al., 2019].

According to Zinchenko Y. et al. (2019), trigger anamnestic factors include professional contact with printers, as well as severe prolonged stress and a history of more than 3 pregnancies.

According to official sources, today more than 4 million toxic substances are registered in the world and their number increases by at least 6000 annually [Nikolaev A.V., Churilov L.P., 2020, Skepyan N.A., 2000; Koshkina V.S., Medvedeva Yu.G., 2011]. These substances can have a direct toxic effect on the cells of the body, and when they die, they produce autacoids that trigger inflammation mechanisms and, in accordance with the “danger hypothesis” of P. Matzinger, through increased expression of costimulatory molecules on immune cells and prolongation of the existence of immunosynapses, have the ability to expand the spectrum of autoimmunity and increase the titers of autoantibodies [Nikolaev A.V., Churilov L.P., 2020, Fuchs E.J., Matzinger P., 1996].

When cells are altered by toxicants, neoantigens can be formed, to which the individual's lymphocytes are not tolerized, which stimulates immunopathological processes.

On the other hand, in the process of transformation and neutralization of xenobiotics in the body, not only substances devoid of toxic properties are formed, but also the so-called reactive compounds, mainly of an epoxy and anoxic nature, with free radical properties (“membrane-attacking complexes”), interacting with cell membranes, nucleic acids, proteins with the formation of neoantigens, membrane toxins and even carcinogens (mutagens). A number of them, providing trigger and adjuvant effects, activate mediator systems of inflammation, cause allergoic reactions and accumulation of pro-inflammatory autacoids [Nikolaev A.V. et al. 2020, Churilov L.P., 2021; Connor M.R., Stevens R.S., 2012]. That is why the increase in environmental pollution and the growth of chemical load on humans are associated with an increase in adjuvant effects, allergic, allergoic and autoimmune diseases. Allergy, including drug allergy, occurring in at least 20% of the population, is accompanied by endogenous intoxication (EI), that is, excessive systemic action of autacoid biologically active substances (BAS),

which largely determine the severity of dysfunction of the natural detoxification organs (NDO) , in particular, the liver, kidneys, lungs [Nikolaev A.V., Churilov L.P., 2020, Churilov L.P., 2021; Jojua T.V., 2018]. Last but not least, this is why the incidence of certain autoimmune diseases in different regions of the Russian Federation over the past few years has been tenfold different and correlates with factors of the urban environment, in particular, the road complex [Nikolaev A.V. et al. 2020, Soprun L.A. et al., 2018].

There are studies that, in general, among smokers, PS was less common than among non-smokers, but it is in smokers that dysfunction and interstitial changes in the lungs in sarcoidosis are more pronounced, and the diagnosis is made late, since PS passes "under the guise" of other diseases [Bagisheva N.V. et al., 2017; Mise K. et al., 2011; Julian M. W. et al., 2013]. In smokers, pulmonary macrophages and the immunomodulatory effect of nicotine prevent T-lymphocytic infiltration in the lungs and, therefore, extrapulmonary manifestations of sarcoidosis are more often noted [Nikolaev A.V. et al. 2021, Bindoli S. et al, 2016].

The most likely hereditary factors of the disease include genetic features of the regulation of the immune response, which increase the risk of developing a number of classic autoimmune diseases: haplotype variants of the human major histocompatibility complex (HLA); TNF-alpha gene polymorphisms; angiotensin-converting enzyme (ACE); vitamin D receptors (VDR), etc. [Nikolaev A.V. et al. 2021, Morgenthau A.S. et al., 2011; Oswald-Richter K.A. et al., 2012; Starshinova A.A. et al., 2019; Dvornikova K.A. et al. 2020].

In recent years, clinical manifestations in TS due to the variety of etiological factors (from mycobacteria to xenobiotics) are considered by some scientists as similar to the autoimmune / autoinflammatory syndrome caused by adjuvants (ASIA - Autoimmune / Inflammatory Syndrome Induced by Adjuvants) [Nikolaev A.V. et al. 2021, Shoenfeld Y., Agmon-Levin N., 2011; Starshinova A.A. et al. 2019; Zinchenko Y. et al., 2019]. This syndrome includes 5 autoimmune disorders: post-vaccination syndrome, siliconosis, macrophage myofascial

syndrome, Gulf War veterans' syndrome, and "unhealthy" buildings syndrome. At the same time, the development of autoimmune inflammation is preceded by hyperstimulation of the immune system due to the contact of people with trigger factors (adjuvants) in the presence of an individual genetic predisposition. Mechanisms of autoimmunity induction may be different, in the tissues there are pathomorphological signs of immune inflammation - lymphohistiocytic infiltration, granulomatous inflammation, scleroderma-like changes. A characteristic feature is the regression of clinical, laboratory and pathological manifestations after cessation of contact with the adjuvant [Nikolaev A.V. et al. 2021, Radenska-Lopovok S.G., Volkova P., 2018].

In separate scientific studies and literature reviews, it is emphasized that sarcoidosis is often combined with other autoimmune diseases (chronic autoimmune Hashimoto's thyroiditis, Sjögren's syndrome, autoimmune rheumatological lesions, immunopathological vasculitis, etc.). It is associated with certain features of the major histocompatibility complex haplotype (HLA; HLA-DRB1*0301, HLA-DQB1*0201, etc.), with possible autoantigens (in particular, vimentin). In sarcoidosis, autoantibodies to vimentin, peptides from the composition of lysyl-tRNA synthetase and ATP synthase, zinc finger protein 688, protein of mitochondrial ribosomes L43, etc. have been registered. Mtb-HSP65 and Mtb-HSP16, mycobacterial katG protein, acne propionic acid bacteria antigens). Sarcoidosis is associated with the presence of lymphocytic infiltration of affected organs; sarcoid granulomas contain lymphocytes of different subpopulations and regress with immunosuppressive therapy. The disease is also characterized by features typical for autoimmunopathies of subpopulation spectra of lymphocytes in the blood [Ershov G.A. and Churilov L.P., 2017; Zinchenko Yu.S. et al., 2017; Nikolaev A.V. et al. 2020, Starshinova A.A. et al., 2019; Fernandes S.R. et al., 2000; Celada L.J. et al., 2015; Bindoli S. et al., 2016; Zinchenko Y. et al., 2019; Starshinova A.A. et al., 2019; Baerlecken N. et al., 2020; Kudryavtsev I. et al., 2020].

According to A.A. Starshinova et al. (2019), all of the above signs are only indirect evidence of the autoimmune nature of inflammation in PS, while the direct criteria for autoimmune diseases could include their experimental reproduction by the action of isolated human autoantibodies, including during transplacental passage from the mother, or when detected in vitro specific autoantigen [Rose N.R., Bona C., 1993].

According to Yu.S. Zinchenko et al. (2019), in the blood of patients with PS after their stimulation with recombinant tuberculosis allergen antigens (ESAT-6/SFP-10), CIs were not detected, but the latter were detected after stimulation with “lung tissue extract” antigens. This, according to the authors, does not speak in favor of the role of MBT in the development of sarcoidosis and indicates an autoimmune reaction to one's own lung tissue in PS.

In another study, the presence of CI in the blood was studied in patients with PS, PT and healthy people using the dynamic light scattering method with the addition of healthy lung tissue antigens and specific antigens ESAT-6 and SFP-10 in vitro. The significance of the method was 100% for PS and 92.2% for PT [Starshinova A.A. et al., 2020].

Thus, although PS is less common than PT, due to an increase in the incidence, the significance of its study is increasing. Since the 70s of the last century, despite the difference in the course of these diseases, their completely different epidemiological danger and unequal prognosis for life, many researchers have tried to prove the clinical and pathophysiological commonality of tuberculosis and sarcoidosis as granulomatous diseases based on chronic inflammation, controlled mechanisms of delayed-type hypersensitivity (DTH) [Ilkovich M.M. et al., 2014; Nikolaev A.V. et al. 2020, Belokurov M.A. et al., 2018; Chen E.S., Moller D.R., 2015].

At the same time, components of mycobacteria and antibodies to them were found in a number of patients with sarcoidosis, which served as a reason for prescribing anti-tuberculosis therapy [Scadding J.G., 1960; Nikolaev A.V., Churilov L.P., 2020, Moscovic E.A., 1978; Khomenko A.G. et al., 1996].

At present, the role of MBT as the main etiological factor in sarcoidosis has not been confirmed. But the concept of tuberculosis and sarcoidosis as two variants of the response of the body's reactivity to close or even identical etiological factors (perhaps on a different mosaic-permissive background) is not rejected and finds supporters [Nikolaev A.V. et al. 2020, Hörster R. Et. Al., 2009; Gupta D. et. al., 2012; Agrawal R. et. al., 2016].

1.2 The role of immunological mechanisms in the pathogenesis of tuberculosis and sarcoidosis of the lungs

1.2.1 Pulmonary tuberculosis

The main entrance gate for MBT tuberculosis is the respiratory tract, and the elements of the innate, nonspecific immunity system (phagocytes) take the main blow, protecting the body, in the place of massive death of which the formation of productive inflammation begins. As inflammatory changes increase, under the influence of cytokine signals, macrophages transform into epithelioid cells, which merge and form Pirogov-Langhans giant cells. In the central part of the giant cell granuloma there is a focus of necrosis, surrounded by a shaft of alveolar macrophages (AM), lymphocytes and epithelial cells, which is associated with the transition of the disease to the chronic stage.

Innate immunity provides a benign course of primary infection in most children and adolescents: only in 5-10% of cases, tuberculosis develops in one form or another [Trinchieri G., Sher A., 2007].

Primary (congenital or acquired) immunodeficiency in patients with PT is extremely rare, but extremely often - up to 80-90% - patients show certain features of secondary immune deficiency, which at the beginning of the disease serves as one of the factors in its development, and then - and a consequence of the disease, forming a vicious circle [Dheda K.A. et. al., 2010].

But MBTs adapt well in the human body, persisting inside macrophages after their absorption, preventing the bactericidal effect of the final phase of phagocytosis (due to their antioxidants, proteins that disrupt the metabolism of the active form of vitamin D, phagocyte repellents, etc.), as a result of which the infection proceeds latently and often is detected only by immunological studies [Borisova M.I., Savitskaya N.G., 2015; Churilov L.P., 2021; Ferguson J.S., et al., 2006; Heemskerk Dorothee et al., 2015]. Immunity in this case is of a “non-sterile” nature, and with the appearance of favorable immunosuppressive conditions (chronic stress, hypovitaminosis, malnutrition, poor environmental and social conditions, concomitant diseases, etc.), reinfection or activation of MBT persisting in the cells of the immune system is possible with the development of the clinic when the infection spreads with blood to various organs and tissues of the body [Starshinova A.A. et al., 2019]. That is, a relatively small part of people fall ill with progressive PT, and the outcomes of infection and illness depend on the degree of individual relative natural resistance, which is formed by protective barriers (skin and mucous membranes), bactericidal substances (on the skin and mucous membranes, in secrets), protective reflexes (cough to remove foreign particles or bacteria from the respiratory tract), factors of the innate immunity system (paleoimmunity), etc. [Churilov L.P., 2021; Demidik S.N., Wolf S.B., 2016].

In any case, alveolar macrophages (AM) serve as the first line of defense against MBT in the lungs - through phagocytosis, exocytosis of bactericidal agents, antigen presentation, stimulation of T-lymphocyte accumulation in the focus of inflammation, etc. [Ernst J.D., 1998; Chen E.S. et al., 2010]. At the same time, there are specific mechanisms for binding MBT to phagocytes through the receptor apparatus of the latter, including various receptors: complement (CR1, CR3, CR4), mannose, surfactant proteins, Toll-like, MSR-receptors of "scavengers", etc. [Dheda K.A. et. al., 2010]. The cytokine IFN-$_\gamma$ inhibits the expression and function of these receptors, leading to a decrease in the adhesion of mycobacteria to macrophages, and the cytokines of T-helper type 2, in

particular, IL-4, as well as the eicosanoid autacoid PgE2, stimulate the expression of receptors [Julian M.W. et al., 2013].

Once in the phagosome, MBT, as a result of the fusion of phagosomes with lysosomes, are exposed to the action of active oxygen- and halogen-containing radicals, nitric oxide, and other inflammatory mediators. These reactions are mediated by complex cytokine-mediated interactions between lymphocytes and phagocytes. It is possible that the ability of MBT to avoid the toxic effects of oxygen and nitrogen reactive radicals is a key step in the transition to the latent stage of infection [Trinchieri G., Sher A., 2007].

In addition to AM, dendritic, mast cells, and epitheliocytes participate in defense against MBT, the activation of which through the system of Toll-like receptors leads to the release of a number of cytokines (TNF-a, IL-1, IL-6, IL-8, IL-22, IL -23) and chemokines. This, in turn, promotes chemotaxis to the site of infection of neutrophils and lymphocytes, the activation of which occurs in the lymph nodes, where some of the antigen-loaded macrophages and dendritic cells (DC) migrate. Like macrophages, neutrophils interact with MBT and realize their bactericidal potential through the so-called "oxidative explosion", as a result of which activated oxygen species (AOS) appear, initiating the process of lipid peroxidation (LPO) in the membrane structures of the pathogen with their subsequent destruction. In addition, leukocytes and epitheliocytes under the influence of IL-22 produce animal antibiotics - defensins.

In this case, enzymatic and free-radical damage is possible not only to the microorganism, but also to the phagocytic cells themselves, which have their own enzyme system of antioxidant protection (AOD) to varying degrees [Brazhenko N.A., Brazhenko O.N., 2017; Ufimtseva E.G. and others, 2019; Churilov L.P., 2021; Dubaniewicz A. et al., 2012]. In the acutely progressive course of PL, the activity of this system is significantly reduced, which leads to chronic infection [Kumar R. et al., 2012].

The reproduction of MBT in the body of experimental animals is delayed due to the physicochemical characteristics of tissues with properties that are

unfavorable for this process. For example, fatty acids of the aliphatic series have a bacteriostatic effect, they are sufficient to delay the reproduction of the MBT of the human type, and for the bovine type, the concentrations should be much higher. Free fatty acids, especially unsaturated ones (oleic and linoleic), have a strong mycobactericidal activity, inhibit the enzymatic activity of mycobacteria [Mishin V.Yu. et al., 2015].

The regulation of functions and differentiation of macrophages is determined by the production of inflammatory autacoids in the form of prostaglandins E2, F2, cytokines and chemokines. The level of their production depends on the activity of enzymes structurally associated with mitochondria, lysosomes, cytosol and endosomal proteases of cells of the macrophage system [Alonso S., et al., 2007; Li Q.H. et al., 2012].

Reactive forms of nitrogen inhibit the viability of MBT even more effectively. Nitric oxide is not only a vasodilator exudation mediator, but also a free radical synthesized from L-arginine with the formation of two new compounds - NO and citrulline. The main reactions of nitric oxide are interactions with oxygen, oxygen radicals (superoxide anion) and metal compounds with variable valence. The final stable products of the reaction of nitric oxide with oxygen are nitrites and nitrates, their levels in the blood of patients with PT decrease in parallel with the increase in the severity of the process [Valiev R.Sh. et al. 2017], which, however, is unlikely to be significant, because this autakoid - local and zonal action, respectively - is primarily important for its intraorgan focal concentrations [Churilov L.P., 2021]. In infiltrative processes, compared with focal processes, the concentration of nitric oxide metabolites in neutrophils is increased, and in fibrous-cavernous tuberculosis, its generation is inhibited. With an acutely progressive course of PT, the basal level of nitric oxide in mononuclear cells rises sharply, then the functional reserves of cells are depleted [Valiev R. Sh., Valiev N. R., 2017].

In patients with PT, there is a very low activity of monocyte enzymes that depend on reduced forms of nicotinamide adenine dinucleotide (NADH and

NADH2), which cause the formation of reactive oxygen species needed to complete phagocytosis. Violation of the metabolic processes of monocytes is combined with a sharp increase in the synthesis of prostaglandins (especially PgE2) and pro-inflammatory cytokines with the recruitment of an additional number of leukocytes [Marchiori E. et al., 2010].

The resistance of phagocytes to intraphagosomal MBT is one of the main deterrents in protection against tuberculosis. At the same time, the response of the adaptive immunity system, initiated by the antigen with the help of clones of specific immunocompetent lymphocytes and their soluble products (antibodies, lymphokines), in close interaction with nonspecific defense factors [Divangahi M. et al., 2008], is of great importance in preventing the spread of infection.

With the normal functioning of innate immunity, it seems that the participation of specific adaptive immunity for protection against MBT is not necessary. However, with immunodeficiency, with a decrease in the function of AM and neutrophils for various reasons, it is triggered by dendritic cells with the appearance of type 1 T-helpers (Tx1; T-cell immunity). The main function of this defense mechanism is the organization and maintenance of granuloma formation around infected macrophages [Divangahi M. et al., 2008]. The latter are less effective in triggering the primary response and are more often associated with the formation of Th2 (B-cell, humoral immunity). It is believed that B cells serve as inducers of a secondary immune response with the development of both invasive processes and hypersensitivity to MBT [Carranza C. et al., 2006].

Thus, certain macrophages and DCs are not only phagocytes, but also antigen-presenting cells of the immune response, combining the innate and antigen-specific adaptive immune systems.

The intercellular contact of macrophages and T-lymphocytes in the so-called immunosynapse, created in regional lymph nodes, where the selection of lymphoid clones affinity for the presented antigen, leads to clonal expansion of lymphocytes of the required specificities and the implementation of the latter specific protective reactions against MBT. At the same time, according to the rule

of immunological clearance, autoimmunity is activated against fragments of destroyed and dying cells of the body [Poletaev A.B. et al, 2012; Gagneux S., 2017].

At the final stages of differentiation, there are functionally different macrophages type 1 (M1), which produce, in particular, the cytokine IL-23 and contribute to the implementation of Th1 (cellular) immunity, as well as macrophages type 2 (M2), which produce IL-10 with access to Th2-dependent type 2 (humoral) type of immunity [Verreck F.A. et al., 2004; Savage N.D. et al., 2008]. At the same time, differentiated Th1 are involved in the activation of CD8+ cytotoxic lymphocytes, and IFN-$_\gamma$ secreted by T-cells and NK-cells (killers) activates macrophages and kills bacteria by increasing intracellular clearance by inducing fusion of phagosomes with lysosomes, as well as enhancing the production of nitric oxide. and oxygen radicals. Activation of the Th2 pathway of immunity leads to enhanced production of antibodies, the most protective in protecting against fragments of decaying cells, extracellular microbes, parasites and their larvae, etc. [MacMicking J.D. et al., 1997; Kaufmann S.H., 2001; Churilov L.P., 2021].

Although today there is no complete information that allows us to finally determine exactly how the choice of the type of immune response and the polarization of macrophages along the M1 or M2 pathways occur, there is a reciprocity of these pathways, when the production of IFN-$_\gamma$ Th1 suppresses the production of IL-4 Th2, and the production of IL- 10 Th2 suppresses the production of IFN-$_\gamma$ Th1. There is information about the predominant polarization of macrophages in tuberculosis along the M1 pathway, although the M2 pathway is also present in tuberculosis, and in the formation of sarcoidosis granulomas, on the contrary, the polarization of the response is significantly shifted to the M2 side [Crouser E.D. et al., 2017].

It has been established that in the infectious process caused by MBT, the relative content of IFNγ-producing cells among Th17 and follicular Tfh peripheral blood is reduced compared to the control [Kudryavtsev I.V. et al., 2019].

It has been shown that MBT stimulates the production of IL-1 β mononuclear cells, as well as tumor necrosis factor (TNF)-alpha, which are involved in the formation of granulomas, cell fusion into multinuclear giant elements, and induction of inflammation [Velayati A.A., Farnia P., 2017]. On the other hand, it was noted that the favorable course of the tuberculous process and effective therapy are characterized by a decrease in the levels of IL-1 β and TNF-α and an increase in the number of cytokines such as IL-2 and interferon-γ (IFN-γ). In other words, MBT consistently trigger stimulation reactions, cell destruction, barrier inflammatory response from the body, focal localization of inflammation in the form of granulomas. With an unfavorable course of the disease, in the presence of immunosuppressive and immunodeficiency factors, necrosis of granulomas and new protective reactions of the systems that regulate inflammation occur, with the formation of a vicious circle.

The barrier of inflammation is broken, excessive systemic penetration of inflammatory autacoids creates general disorders in the body according to the type of acute phase response, and then the symptom complex of tuberculous intoxication, up to cachexia. Such a staging of the process leads to a gradual depletion and loss of life support functions from the lungs and other vital organs [Churilov L.P., 2021; McMillen C.W., 2015].

The response of macrophages to MBT is the launch of apoptosis mechanisms, which is the most important component of effective antimycobacterial protection. Virulent MBT leave it, inducing cell necrosis, followed by uncontrolled reproduction in necrotic tissue. Apoptosis of infected neutrophils contributes to the selective removal of infected cells from the focus of inflammation and enhances the functional activity of tissue macrophages [Davies Peter D.O., 2016]. But the activation of apoptotic processes in the body is fraught with auto-presentation of antigens and neoantigens that are part of apoptotic bodies, which can lead to increased autoimmunity to them [Gaipl U.S. et al., 2007; Poletaev A.B. et al., 2012].

In any case, the combination of invasive-counterimmune effects of MBT and multilevel protection against them are a feature of immunity in tuberculosis. When the infection is reactivated, the body's defense, enhanced by BCG vaccination, can win much faster, but the paradox of the body's immune response to MBT is the simultaneous activation and anergy of certain immunocompetent cells [Tang Y., Stratton C. W., 2018].

In infectious pathology, a typical general pathological process, the so-called acute phase response or acute phase response, occurs, guided by minimal amounts of inflammatory autacoids penetrating the systemic circulation, the meaning of which is the redistribution of the plastic and energy resources of the body in favor of organs and tissues involved in protection against infection. and in minimizing alternative and septic manifestations [Kushner I., 1991; Churilov L.P., 2021]. An important role in its pathogenesis is played by plasma "acute phase proteins" - catalytic and signaling bioregulators that perform systemic protective functions in conditions of local inflammation (C-reactive protein (CRP), haptoglobin, α1-antitrypsin, fibrinogen, fibronectin, hepcidin, ferritin). The appearance in the blood of increased concentrations of these proteins (positive globulins of the acute phase), synthesized mainly in the liver, is an early evidence of the involvement of immunocompetent and phagocytic cells, reflects the severity and nature of infectious and immunopathological processes, the degree of forcing focal inflammatory barriers by autacoids, and inducers of this typical pathological process interleukins 1, 6 and TNF-α produced by macrophages serve [Churilov L.P., 2021; Thillai M. et al., 2017]. The proportionality of the acute phase response in relation to the severity and course of the infectious process is very important. Its moderate, regular course with the consistency of focal barriers of inflammation leads to protective effects, while the excessive hyperergic response of the acute phase with an avalanche-like intake of excess cytokines and other inflammatory mediators into the systemic circulation takes on the character of a toxic-septic shock-like process (for example, a "cytokine storm") and leads to severe violations of the vital functions of organs, even those not directly affected by the

primary foci of inflammation. In this case, the price of protective stereotypes is prohibitively high, and their secondary pathogenicity far exceeds the protective effect [Churilov L.P. 2009, 2015]. A private but striking variant of this course of events is, for example, a pathogenic conflict of local and systemic defense mechanisms in severe coronavirus or influenza infections [Ryabkova V.A., Churilov L.P., Shoenfeld Y., 2021].

With the involutive course of PT, such moderate systemic changes are protective in nature, increasing the bactericidal, antiproteolytic, and anti-inflammatory potential of the body; but the extreme hyperproduction of a number of protein and other bioregulators complicates the course of the disease, including due to the suppression of the phagocytosis function [Perelman M.I., Bogadelnikova I.V., 2015]. A sign of involvement of the adaptive immune system in response to tuberculosis is the delayed-type hypersensitivity reaction (DTH), which is based on the migration of antigen-specific T cells to the site of injection of mycobacterial antigen (an example is tuberculin skin tests, for example, the Mantoux test) [Thillai M et al., 2017].

To strengthen immunity, a program of mandatory anti-tuberculosis vaccination (BCG) was developed in a number of countries, after which specific anti-tuberculosis antibodies are formed within 3 weeks with the formation of a memory of the protective response program [Dietrich J., Doherty T.M., 2009]. It turned out that the live BCG vaccine, persisting in the body of the vaccinated, has a non-specific adjuvant-like (“training”) effect on their immune system, enhancing the immune response not only against MBT, but also against other microorganisms, in particular, leprosy pathogens, as well as, according to the latest data - both coronaviruses, and stimulating antitumor immunity, which was used in the treatment of bladder cancer [Covin C. et al., 2020]. On the other hand, it is these adjuvant effects that contribute to autoimmune and autoinflammatory pathology, with which a number of authors associate sarcoidosis (see above).

MBT do not secrete any exotoxins, endotoxins or histolytic enzymes, and their pathogenicity is associated with the ability to avoid destruction by

macrophages and induce delayed (IV) type hypersensitivity with caseous necrosis. At the same time, three important mechanisms are important in the progression of PT: virulence factors of the microorganism; the ratio of hypersensitivity and immunity to the pathogen; factor of tissue destruction and caseous necrosis [Bagirov M.A. et al., 2018]. Classical sources emphasized the role of early and chronic tuberculous intoxication in the pathogenesis and manifestations of the disease [Korol O.I. et al., 2010]. But, according to modern concepts, intoxication in tuberculosis is a conditional clinical designation for the systemic action of inflammatory autacoids and the immune response during the development of this disease [Churilov L.P., 2021]. Destructive processes in caseous necrosis, characteristic of PT, are associated with increased activity of metalloproteinases. In terms of differences in inflammation in PT and SP, it is significant that, according to the latest data, only in PT (but not in PS), the matrix metalloproteinase 8 (MMP8) gene is overexpressed in lung cells [Chai Q. et al., 2020].

The effectiveness of bactericidal mechanisms noted above depends not only on lytic enzymes, but also on a number of bioregulators, including those associated with vitamin D and its derivatives.

An increase in immunological activity with vitamin D is due to the induction of its active form, calcitriol, the defensin natural animal antibiotic cathelicidin (in humans - LL-37), a powerful antimicrobial peptide and a universal chemokine [Gombart A.F. et al., 2005: Yamshchikov A.V et al., 2010; Blischak J.D. et al., 2015]. At the same time, cathelicidins and, in particular, LL-37 reduce the level of antigenic load by mycobacteria [Clohisy D.R. et al., 1987]. In non-specific pulmonary pathology of an inflammatory nature, the concentration of cathelicidin in the blood of patients is not higher than in healthy people [Lambert A.A. et al., 2014].

Sarcoidosis granulomas, primarily due to their macrophages, which have lipopolysaccharide-stimulated MBT, nitric oxide and IFNγ 1α-hydroxylase, can be a source of additional formation and accumulation of the active form of vitamin

D, which is sometimes manifested by hypervitaminosis D and hypercalcemia in sarcoidosis [Bell N. H. Et al ., 1979; Adams J.S., Ren S.Y., 1996; Conesa-Botella A. et al., 2009]. In tuberculosis, however, hypervitaminosis D is by no means observed; on the contrary, another classic of pediatrics, Academician A.F. Tour emphasized that "tuberculosis and rickets go hand in hand" [Tour A.F., 1966; Martineau A. R. et al., 2007; Noaham K. E., Clarke A., 2008; Chesney R. W., 2010] At the same time, it has been proven that vitamin D in its active form enhances anti-infective immunity, and in higher primates and humans, almost all innate immunity against intracellular parasites is mediated by vitamin D-dependent nuclear receptors (VDR) [Belyaeva I.V.., Churilov L.P. et al., 2013, Liu P. T. et al., 2007]. Currently, direct induction of cathelicidin biosynthesis in human cells by calcitriol and the key relationship of this process with anti-infective resistance have been proven [Wang T.T et al., 2004; Gombert A. et al., 2005; Gombart F., 2009].

On autoimmunity, vitamin D, on the contrary, has a multilevel deterrent effect, and its deficiency contributes to pathological autoimmune manifestations in a variety of autoimmune pathologies [Hewison M., 2010].

Above, the opinion of a number of specialists was indicated that tuberculosis and sarcoidosis are two forms of the same disease with a different response of the immune system to similar etiological factors, which is respectively in a weakened or stimulated state. The similarity of these diseases is associated with the adjuvant-like action of the components of mycobacteria and/or different metabolic states. [Ariel B. M., 2005; Beliaeva I.V., Churilov L.P., et al. 2019, Gupta D. et al., 2007; Agarwal R., Gupta D., 2009]. We suggest that the different state of vitamin D metabolism in tuberculous or sarcoidosis granulomatous inflammation may be of significant importance here. See below for more on the role of vitamin D as a bioregulator.

1.2.2 Sarcoidosis of the lungs

In SL, no toxin-producing pathogen has also been identified, but the above hypotheses (“infectious factors”, “environmental factors”) indicate a possible trigger-adjuvant effect on the immune system, which contributes to the damage of own cells during a protective inflammatory reaction and hyperproduction of inflammatory autacoids.

Dying cells always become sources of inflammatory mediators, some of which enter the systemic circulation, providing the development of an acute phase response, fever, stress, leukocytosis - that is, systemic correlates of moderate, normally occurring inflammation. If the barrier mechanisms of inflammation (slowing of blood flow, stasis, thrombosis, coagulation, demarcation leukocyte wall, etc.) turn out to be untenable, and this happens with a large volume and perimeter of the boundaries of tissue lesions, then pro-inflammatory autacoids (they are also inflammation mediators) in excess penetrate into the systemic circulation and interfere with the regulation of systemic functions, disrupting blood circulation, respiration, metabolism with the possible development of multiple organ failure, shock-like conditions and shock [Churilov L.P., 2009, 2015; Ryabkova V.A., Churilov L.P., Shoenfeld Y. 2021].

In any case, with cell death, local inflammation occurs, and the protective reactions of the whole organism can be weak, moderate, strong, and beyond the intensity, depending on the combined systemic action of inflammatory mediators, tissue decay products, and microflora factors. At the same time, an excessive concentration of many biologically active substances (TNF-α, lipid peroxidation products, etc.), which have toxic properties, in PT and PS contributes to damage, destruction of cells and disruption of the drainage functions of the lymphatic system and neutralization of emerging pathogens, although clinical manifestations are always in the foreground. diagnostic signs of lung tissue damage [Giovinale M. et al., 2009; Hurster R. et al., 2009; Petousi N. et al., 2012]. Because of this, the main condition for the existence of cells of vital organs changes: instead of a

normal flow of microcirculation with the delivery of oxygen, life support products, bioregulators to the cells - with simultaneous evacuation of the products of their vital activity and signals generated by these cells into the lymph and bloodstream, chaos occurs, blockade of microcirculation with violations of these flows, the progression of hypoxia, the topical diversity of regional regulatory processes is disrupted, local and systemic regulators come to a conflict that reduces the effectiveness of adaptation and compensation [Churilov L.P., 2021; Ryabkova V.A., Churilov L.P., Shoenfeld Y., 2021].

In addition to the cytotoxic effect of immune system products and inflammatory autacoids, PT and PS may damage vital organs in hepatoxic and/or nephrotoxic reactions to chemotherapy drugs used in their treatment [Kumar S. S. et al., 2016; Mbelu M.K. et. al., 2018].

Currently, it is believed that the basis of the immunological links in the pathogenesis of SL is the delayed-type hypersensitivity reaction (DTH). The target organs in sarcoidosis are usually the lungs, skin, heart, liver, and less often the central nervous system. [Oswald-Richter K. et al., 2010; Dziadzio M. et al., 2011; Rijavec M. et al., 2011; Adrianto I. et al., 2012; Agarwal R. et al., 2012; Furusawa H. et al., 2012; Silva P.H. et al., 2012; Ten Berge B. et al., 2012; Thillai M. et al., 2012; Dubaniewicz A., et al., 2013].

In the acute phase of HRT development, an antigen that persists in the body and is difficult to destroy stimulates the secretion of IL-12 by macrophages [Wikin M. et al., 2012]. Activation of T-lymphocytes by this cytokine leads to suppression of the cytokine-secreting function of Th2-lymphocytes and to increased secretion of cytokines by Th1-lymphocytes IFN-γ, TNF-α, IL-3, colony-forming factor, which activate macrophages/monocytes, contributing not only to their differentiation and reproduction, but also their migration from the bloodstream to the focus of inflammation [Petereit H.F. et al., 2010; Darlington P. et al., 2012; Merwald-Fraenk H. et al., 2012; Shigemura M. et al., 2012]. The inability to eliminate the antigenic stimulus causes the differentiation of macrophages into epithelioid cells that secrete TNF-α and later some of them merge, forming, with

the signaling role of the latter, multinucleated giant cells [Ahmadzai H. et al., 2012; Hage J.E. et al., 2012].

The granulomatous type of inflammation, which is based on the DTH reaction, is characterized by the activation of T-helper type 1 (Th1-cells) [Dziadzio M. et al., 2011; Hemanth I.K., Binuraj C., 2018]. At the same time, IL-12, which interacts with receptors on the surface membrane of lymphocytes with activation of the synthesis of γ-IFN and differentiation of Th1 cells, is considered as a key cytokine for inducing a cellular immune response in the lungs [Darlington P. et al., 2012; Suchankova M. et al., 2013].

The fundamental features of the response of immunocompetent cells in sarcoidosis granulomas, in comparison with tuberculous ones, are considered by some authors to be the polarization of macrophages, mainly in M2 cells [Crouser E.D. et al., 2017]. Ex vivo model studies have shown that, as a result, significantly less IFNγ and much more TNFα, as well as IFNαβ are produced in the foci of sarcoidosis inflammation, which affects the course of productive inflammation [Sellares J. Et al., 2018].

The rapamycin-sensitive macrophage metabolic checkpoint kinase, the mTOR protein, switches the direction of differentiation of these cells and is inhibited by the TSC2 protein. In mice mutated for the TSC2 protein gene, this kinase is chronically activated, leading to the development of a systemic granulomatous disease similar to sarcoidosis that affects the lungs and skin. In human macrophages from sarcoid granulomas, hyperactivity of the mTOR pathway is found [Linke M. et al., 2017]. Thus, if this model of SL is sufficiently adequate, it confirms that the differences between SL and PT should be sought in the differentiation pathways and signaling spectrum of macrophages in these granulomatose.

In terms of laboratory data, the progressive course of SL is characterized by:

1. High levels of chemokines in bronchoalveolar lavage fluid (BAL) and in BAL cell supernatants, including CXC chemokines (MIP-1, MCP-1, RANTES),

as well as CC-chemokine IL-8. It is these chemokines that are responsible for the recruitment of inflammatory effector cells into lung tissue.

2. Increased levels of expression of IL-2 and IFN-γ, as well as CXCR3, CCR5, IL-12R, IL-18R - by CD4+ lymphocytes. However, it has been shown that the expression level of IFN-γ in PS is inferior to PT [Crouser E.D. et al, 2017; Sellares J. et al., 2018]

3. The level of TNF-α AM synthesis has the greatest prognostic value in relation to the progress of the disease and the formation of pneumofibrosis [Milman N. et al., 2011; Hattori T. et al., 2012; Senturk A. et al., 2012; Tan H.L., Rosenthal M., 2013; Crouser E.D. et al, 2017; Sellares J. et al., 2018].

Of great interest are the issues of participation in the pathogenesis of PS of such a lipid as steroidal vitamin D in the form of a group of biologically active substances (cholecalciferol, ergocalciferol, and others). Cholecalciferol (vitamin D3) is synthesized in humans in the skin under the influence of ultraviolet rays of the “B” range, and also enters the human body with food. Ergocalciferol (vitamin D2) can only be supplied with food [Holick M.F., 2012]. Both substances are actually provitamins or prohormones that are activated in the body as a result of hydroxylation reactions, first in the liver to 25-hydroxy-cholecalciferol (abbreviated as 25 (OH) D3, calcidiol or calcifediol), and then in the kidneys and cells of the immune system, in particular - macrophages, in 1,25-dihydroxy-cholecalciferol (1,25(OH)2D3, calcitriol) [Rao D.S., 1999; Holick M.F., 2012; McCullough P.J., Lehrer D.S., 2018].

In chronic inflammatory and various autoimmune diseases, a person has a deficiency of vitamin D, which is confirmed by a decrease in its concentration in the blood of less than 20 ng / ml [Nnoaham K.E., Clarke A., 2008; Shapira Y. at al., 2010].

According to many researchers, vitamin D deficiency is observed in 1% of the population (<17.5 nmol / l or 7 ng / ml), and insufficiency - in 21-58% (<62.5 nmol / l or 25 ng / ml), depending on age, gender, place of residence [Looker A.C. et al., 2002]. Moreover, this is typical even for sunny countries due to the

domestication of a person who spends all the time indoors. For example, in sunny Israel in the summer, 78% of several hundred surveyed citizens had low levels of vitamin D in the blood [Shoenfeld Y. et al. 2010]. The same picture is typical, according to O.V. Danilenko et al. (2017) and for residents of St. Petersburg and the Leningrad region, and in the summer, and not only in the winter season.

It has been shown that as a result of genetically determined features of reactivity, 86% of African Americans with granulomatous inflammation have vitamin D deficiency, in every second case it is pronounced, at a level of 25-hydroxy-D <10 ng/ml, but the level of its active form is 1 , 25-dihydroxyvitamin D (calcitriol), usually normal [Uitterlinden A.G. et al., 2004].

The effect of calcitriol is manifested in the maintenance of calcium levels in a narrow range together with parathyrin (according to the old nomenclature - parathyroid hormone, PTH) [Nimi et al., 1999]. A decrease in serum calcium levels causes the release of PTH, which increases the expression of 1α-hydroxylase in the cells of the renal tubules with the occurrence of a hydroxylation reaction of 25-hydroxyvitamin D and an increase in the level of calcitriol, contributing to the return of calcium levels to the normal range through stimulation of intestinal absorption and renal reabsorption of this cation. Calcitriol inhibits the further release of PTH and 1α-hydroxylase, preventing the development of hypercalcemia [Shrayyef M.Z. et al., 2011]. However, in macrophages, unlike in the kidneys, 1α-hydroxylase, which converts the precursor to the active form of vitamin D, is insensitive to this inhibitory feedback mechanism, which creates a risk of hypercalcemia and excess calcitriol during macrophage activation [McCullough PJ, Lehrer DS. 2018]. References have already been made above to data on the regular hyperfunction of the macrophage system in relation to the production of calcitriol in sarcoidosis, which is often accompanied by hypercalcemia. Vitamin D modulates the levels of calcium and phosphorus through their binding to a receptor that has a high degree of affinity for calcitriol [Hewison M., 2010]. After binding of calcitriol in the presence of

cofactor retinoid X-receptor (RXR), this ligand-receptor complex binds to various vitamin D-responsive gene elements.

In turn, these genes activate or suppress the activity of a number of proteins involved in bone metabolism, including osteocalcin, calbindin, CYP24A (24-hydroxylase) or CYP27B1 (1α-hydroxylase), as well as PTH [Jones G. et al., 1998]. Thus, vitamin D actually serves as a hormone-vitamin or, in modern terminology, a vitamin. The distribution of vitamin D receptors includes major target organs in the bones, kidneys, and intestines. But these same receptors with low expression are found in monocytes, macrophages, and lymphocytes, and when these cells of the immune system are activated, the expression of vitamin D receptors (VDR) increases significantly. The production of calcitriol increases in monocytes when they are cultivated with cytokines IFN-γ, TNF-α, as well as IL-1 and IL-2 [Zuckerman S.H., Schreiber R.D., 1988; Griffin M.D. et al., 2000; Penna G., Adorini L., 2000; Veldman C.M. et al., 2000] and decreases under the influence of anti-inflammatory dexamethasone [Stoffels K. et al., 2006].

Hansdottir S. et al. (2008) found that human bronchial epithelial cells produce 1α-hydroxylase mRNA and calcitriol without stimulation. The consequence of this synthesis and subsequent binding of VDR to cell chromatin by calicitriol is the expression of the antimicrobial defensin LL-37 (human cathelicidin) and the secretion of soluble CD14. The former serves as a natural animal antibiotic (see above), while the latter detects pathogen-associated molecular complexes, in particular, lipopolysaccharides in the cell walls of gram-negative organisms, including MBT [Yim S. et al., 2007].

A compensatory increase in the body's level of the active form of vitamin D - calcitriol - is necessary to increase the antimicrobial activity of immune system cells [Zadshir A. et al., 2005]. Experiments have shown that vitamin D also modulates the activity of T-lymphocytes, affecting the clinic of sarcoidosis [Chen E.S. et al., 2008; Kojima K. et al., 2012].

In addition, calcitriol reduces the production of IL-12 by macrophages, causes a decrease in the level of IL-2 and positive autoregulation of Th1-cell

activity by cytokines [Gregori S. et al., 2001; Hede J. et al., 2009; Furusawa H. et al., 2012]. It has been established that calcitriol is formed at sites of granulomatous reactions in SL [Liu E.T. et al., 2006; Chakravarty S.D. et al., 2012; Hyldgaard C. et al., 2012; Saussine A. et al., 2012; Richmond B.W. et al., 2013].

It has been proven that AMs are able to spontaneously synthesize calcitriol under the control of IFN-γ or LPS, the content of which in the lungs in SL is increased and contributes to the persistence of inflammation caused by Th1 cells [Dusso A.S. et al., 1997; Kucejko W. et al., 2009]. The level of calcitriol in the blood is a generally accepted test-marker of ongoing inflammation that supports the granulomatous reaction [Infante J.R. et al., 2002].

Thus, vitamin D is the most important component with immunomodulatory effects involved in the pathogenesis of both PT and PS. But it was said above that the direction of differentiation and signaling spectra of macrophages in these granulomatosis are different. In this regard, we note once again that hypervitaminosis D is possible in PS (this does not happen in PT), and it has been proven that vitamin D in its active form enhances anti-infective immunity and suppresses autoimmunity.

If PS and PT are two patterns of response to similar etiological factors with different reactivity of the organism, then is it not the difference in the state of the cytokine-hormone-vitamin D-cathelicidin system that determines the choice of the response pattern? [Belyaeva I. V., Churilov L.P., et al 2017].

In general, the presented literature data indicate many similar features of the pathogenesis of PT and PS - in both cases, there is an excessive systemic effect of autacoids and decay products that arise in the lesions, causing a violation of the systemic functions of the body according to the type of acute phase response, and in severe course - according to the type shock-like state (according to classical terminology - endotoxicosis).

There is much in common in PT and PS and in the course of local productive granulomatous inflammation. It can be generated by the reaction of

the immune system to mycobacterial and other microbial antigens, which gives rise to individual authors to interpret these diseases as 2 forms of the same disease with different immunoreactivity of the body [Ilkovich M.M. et al., 2014; Belokurov M.A. et al., 2018; Gupta D., 2009; Guan H., Ali S.Z., 2011; Gupta D. et. al., 2012; Chen E.S., Moller D.R., 2015; Agrawal R. et. al., 2016]. These differences may be associated with the direction of polarization of macrophages and T-helpers, the peculiarities of the spectrum of cytokines, and the state of the normonovitamin D system and the natural antibiotics dependent on it, in particular, cathelicidin [Irina V. Belyaeva, Leonid P. Churilov,et al 2023].

In dynamics, in patients with PT and PS, the development of systemic multiple organ disorders is observed, which significantly reduces the quality of life and worsens the prognosis of diseases [Starshinova A.A. et al., 2019].

Only a comprehensive examination of patients with PT and PS using clinical, biochemical, immunological, hormonal tests, toxicograms, the study of the state of vitamin D-dependent regulation, the level of cathelicidin and the spectrum of cytokines with instrumental and radiological diagnostic methods can fully characterize the relationship, similarities and differences of the discussed granulomatous disease.

1.3 Clinical and diagnostic features of pulmonary sarcoidosis in the differential diagnostic context

The clinic of PT and its modern pathomorphosis are widely and in detail described in the literature [Perelman M.I. et al., 2010; Galinskaya L.A., 2013; Shilova M.V., 2014; Mordyk A. V., 2015; Kaminskaya G.O., Abdullaev R.Yu., 2016; Podgaeva V.A., 2016; Turchenko S.Yu., 2017; Shprykov A. S., 2017; Ergeshov A. E. et al., 2017; Babalola M.O., 2015; Chipo M. et al., 2016; Grosset J.H., Chaisson R.E., 2017; Gayadhar M., et al., 2019]. Therefore, in this section, it is appropriate to focus on clinical and laboratory signs that are closely related to the topic of this study and the differential diagnosis of PT and PS, in particular,

vitamin D-dependent metabolic parameters, radiation and morphological diagnostic methods.

In tuberculosis, in general, there is, as a rule, a lower level of vitamin D in the blood than in healthy individuals [Beliaeva I.V., Churilov L.P.., et al 2017, Beliaeva I.V., Churilov L.P.., et al. 2018, Nnoaham K.E., Clarke A., 2008]. However, we must not forget that this is a granulomatous disease, like sarcoidosis and non-tuberculous mycobacterioses. The abnormalities of vitamin D metabolism in cells of the immune system, macrophages and lymphocytes that synthesize calcitriol, which are characteristic of productive inflammation controlled by HRT mediators, described above, can exist to some extent in all these granulomatosis [Cadranel J. Et al., 1990]. Therefore, sometimes with LT (in different studied cohorts of patients - from 2 to 50% of cases) with tuberculosis (most often - with combined damage to organs, including the kidneys, as well as in the elderly, with some racial specificity - in Caucasians more often than in Mongoloids and Negroids, especially in populations actively using prophylactic nutritional supplements with vitamin D), both hypercalcemia and an increase in the level of calcitriol in the blood were recorded. Hypercalcemia was also detected in some cases of atypical mycobacteriosis [Abbasi A.A. et al., 1979; Need A.G. et al. 1980; Sharma S.C., 1981; Kitrou M.P. et al. 1983; Lind L., Ljunghall S., 1990: Tan T.T. et al., 1993; Chan T.Y., 1997; Liam C.K. et al., 1998; Roussos A. et al. 2001; Dosumu E.A., Momoh J.A., 2006; Chan J.Y., Kanthaya M., 2015: Kuthiah N., Chaozer E., 2019; Wada T. et al., 2019].

A recent large-scale retrospective study in South India revealed an incidence of hypercalcemia in tuberculosis of about 20%, and the risk factors were concomitant diabetes mellitus, disseminated nature of the disease, and, in particular, renal failure, since calciuria is the leading compensatory mechanism in hypercalcemic syndromes [John S.M. et al., 2020]. Thus, although hypercalcemia occurs in tuberculosis, it, without additional aggravating factors, does not serve as a typical manifestation of PT.

About PS, which is considered the “great imitator”, the amount of knowledge is less and many authors emphasize that the clinical signs of sarcoidosis are diverse, and the lack of informative diagnostic tests makes non-invasive diagnosis difficult, and this contingent of patients can be observed by different specialists for a long time [Baughman R.P. et al. 2001; Little B.P., 2015].

In Russia, the management of patients with identified PS was the same as in PT until 2003, and they were under the supervision of specialists from anti-tuberculosis dispensaries - phthisiatricians.

Currently, this practice is recognized as irrational and patients are transferred under the supervision of general practitioners [Chuchalin A.G. et al., 2014]. At the same time, both in the world and in our country, the main proportion of patients with PS is still detected by chance, during X-ray studies during a physical examination (up to 60%) or when actively contacting a doctor about articular, skin, eye, kidney, neurological complaints [Kharlap S.I. et al., 2012; Costabel U. et al., 2007; Pavic M. et al., 2008; Marak C.P. et al., 2013; Basantsova N. Y. et. al., 2018]. Moreover, until 2003, every third patient with PS underwent trial anti-tuberculosis therapy with isoniazid against the background of systemic corticosteroid therapy [Koth L.L. et al., 2011; Curone M. et al., 2013].

The recent observation of Iranian doctors describing the case of a civil air ambulance pilot who was in contact with patients with a new coronavirus infection and was hospitalized with complaints of shortness of breath, weakness, fatigue and fever with a diagnosis of COVID-19. During an in-depth examination against the background of negative tests for coronavirus, SL was diagnosed for the first time in the acute stage [Momenzadeh M. et al., 2020].

PS and other localizations are usually accompanied by hypercalcemia and, more often, calciuria [Podwysocki B., 1994]. It often reveals signs of endogenous hypervitaminosis D, especially calciuria. A recent study by Polish authors estimates its occurrence in SL at 1/3 of all patients, emphasizing that this imposes restrictions on the use of vitamin D-containing agents for the prevention of osteoporosis associated with corticosteroid therapy in PS in such patients

[Kempisty A. et al., 2018]. Their opinion about the riskiness of preventing osteopenia with vitamin D in sarcoidosis is not shared by the Dutch authors, who found that the lower the level of calcifediol in the blood of patients, the higher the activity of the process in sarcoidosis [Kamphuis L.S. et al. 2014]. But American authors indicate that in sarcoidosis, despite the low level of calcifediol, the level of its derivative calcitriol may increase along with the risk of hypercalcemia and report that the latter is more common in those patients with SL who use vitamin D-containing drugs, and kidney damage increases the risk of hypercalcemia in sarcoidosis by more than 4 times [Sodhi A., Aldrich T., 2016]. With advanced forms of sarcoidosis with renal insufficiency, the frequency of calcium metabolism disorders increases even more [Mahevas M. et al. 2009].

According to Japanese authors, the major histocompatibility complex haplotype of patients with SL can determine the degree of hyperproduction of calcitriol and hypercalcemic manifestations in them [Fujita A. et al., 1995]. This indicates the relationship between immunological and endocrine regulation in SL.

Currently, in world and domestic practice, PS is divided into 5 stages (from 0 to IV), in accordance with the modified classification of K. Wurm (1958), which took into account only the radiographic manifestations of the disease: stage 0 - no changes on the chest radiograph (occurs in 5% of all cases); stage 1 - lymphadenopathy of the intrathoracic lymph nodes; lung parenchyma is not changed (50%); stage 11 - lymphadenopathy of the intrathoracic lymph nodes; pathological changes in the lung parenchyma (30%); stage 111 - pathology of the pulmonary parenchyma without lymphadenopathy of the intrathoracic lymph nodes (15%); stage 1V - irreversible pulmonary fibrosis (20%) [Wizel A.A. et al., 2004; Chuchalin A.G. et al., 2014; Juniarti N., Evans D., 2011].

Sarcoidosis also affects the endocrine glands. These authors put them in third place after the bronchopulmonary apparatus and skin in terms of frequency of involvement, noting that in descending order of frequency there are sarcoidosis of the pituitary gland, hypothalamus, which in domestic practice are often referred to as neurosarcoidosis [Pushkarev M.S. et al., 2019], as well as the thyroid and

parathyroid glands. Thus, combinations of Hashimoto's autoimmune thyroiditis and sarcoidosis of the thyroid gland have been repeatedly described [Sasaki H. et al., 1987; L'Her E. et al., 1995].

With an acute or subacute onset of the disease, in its debut, there is an increase in body temperature for several days (sometimes up to 2-3 weeks), arthralgia, general weakness, some enlargement of peripheral lymph nodes, manifestations of erythema nodosum, localized most often on the legs [Patterson K.C. et al., 2012]. The combination of an increase in intrathoracic lymph nodes with erythema nodosum, joint pain and fever for several days is described as Löfgren's syndrome and probably reflects a pronounced systemic effect of inflammatory mediators (hyperautacoidemia) and a vasculitic component of the disease [Reich J.M., 2012].

Subsequently, there may be an increase in ESR, leukocytosis, lymphocytopenia (less often lymphocytosis), monocytosis. As already noted, often with TS, the content of ionized calcium in the blood is increased, and in parallel with this, positive globulins of the acute phase - CRP, etc. [Zoumot Z., Mann B.S., 2011; Freeman A.M. et al., 2013; Kalkanis A., Judson M.A., 2013].

Enlargement of intrathoracic lymph nodes in TS is often asymptomatic; only some patients develop cough, chest discomfort [Faehling M. et al., 2012].

Percussion and auscultation of the chest are not informative enough. Only with a significant increase in the mediastinal lymph nodes can a shortening of the percussion sound in the interscapular space (in the projection of the roots of the lungs) be determined, and with compression or damage to the bronchi, the appearance of dry wheezing. Sometimes bronchial stenosis develops with the presence of hypopneumatosis, clinical and radiological signs of atelectasis of the corresponding area of the lung tissue [Ganguly S., Ganguly D., 2012].

Bronchial obstruction in PS can occur as a result of narrowing of the lumen of the bronchial tree during the formation of granulomas, deformation and cicatricial fibrosis in small bronchi, as well as compression of the bronchi by enlarged intrathoracic lymph nodes [Martusewicz-Boros M.M. et al., 2012]. The

degree of bronchial obstruction does not always correlate with the x-ray stage of the process [Bargagli E. et al., 2013; Jin X. et al., 2015]. General symptoms of "intoxication" (that is, the systemic action of inflammatory autacoids - see above): weakness, subfebrile condition, changes, hemograms, etc.) development and pulmonary fibrosis, signs of respiratory failure appear with a decrease in lung capacity (VC), [Kucejko W. et al., 2009; Beegle S.H. et al., 2013].

In some patients, sarcoid pleurisy joins, X-ray examination often reveals pleural layers - residual changes in the transferred pleurisy [Darugar A. et al., 2011; Terasaki F. et al., 2012]. It should be noted that diagnostic errors in SL can be up to 75–80%, and the analysis of the entire set of data contributes to the correct diagnosis [Aleksandrovsky B.P., Barenboim A.M., 1973; Huseynov G.K., 2014; Balasubramanian A. et al., 2018].

In recent years, in the differential diagnosis of lung diseases, the method of studying fluid in BAL has been widely used, but the data are highly inconsistent, depending on the duration of the process, the prevalence of productive or exudative type of inflammation, etc. [Urbankowski T. et al., 2012].

There is an opinion that it is almost impossible to distinguish disseminated PT and PS by the cytological picture of BAL fluid, since lymphocytosis, characteristic of sarcoidosis, occurs in 70% of patients with tuberculosis, and epithelioid and giant multinucleated cells, respectively, in 13.0% and 9.1% patients [Lovacheva O.V., Evgushchenko G.V., 1998]. At the same time, this study is widely used, and more and more new bioregulators in the BAL content (endostatin, cachexin, etc.) are being studied [Oswald-Richter K.A. et al., 2012; Oki M. et al., 2013; Naumnik W. et al., 2015].

A valuable method of screening immunodiagnostics is a non-competitive enzyme-linked immunosorbent assay using the ELISA test (short for ELISA - Enzyme Linked Immuno Sorbent Assay). The idea of this approach is based on the theory of immunological clearance of P.N. Grabar - I.E. Kovalev [Kovalev I.E., Polevaya O.Yu., 1985; Grabar P., 1975].

According to S.V. Skurydin et al. (2010) laboratory ELISA method ELI-Pulmo-Test can be used for early diagnosis of lung parenchyma damage (increase in the level of antipulmonary AAB), monitoring the effectiveness of pharmacotherapy (decrease in AAB level) with the assessment of individual treatment regimens and prognosis of the development of chronic lung diseases in X-ray patients negative patients.

The main unifying feature of PT and PS is the syndrome of bilateral dissemination, detected by X-ray examination, which pathologically manifests itself as granulomatous inflammation, although the histological picture of the biopsy does not always allow full confidence in the accuracy of the clinical diagnosis [Wanat K.A. et al., 2013; Zhang C. et al., 2015]. Above, we have already discussed the non-absolute criterion for the presence or absence of necrosis in granulomas and the existence of intermediate between sarcoidosis and tuberculosis patterns of granulomatosis.

Regardless of etiology, all granulomas (in PT, PS, leprosy, berylliosis, etc.) are, to a certain extent, histogenetically similar, and the main cell types in them are represented by macrophages, mononuclear cells, phagocytes, descendants of the monocytic cell line originating from a bone marrow stem cell, and in the latter case, these cells develop from a monoblast to a promonocyte and a monocyte [Modrzewska K. et al., 2009; Reich J.M., 2012].

From the bone marrow, monocytes enter the general circulation, the capillaries of tissues and organs, then migrate into the tissues through the wall of the venular knee of the microvasculature. Here, monocytes are transformed into fixed resident macrophages, acquiring a number of new qualities. During the formation of granulomas, monocytogenic macrophages of hematogenous origin accumulate in the lesion and gradually transform into epithelioid cells, which are considered as markers of the participation of the immune mechanism in granuloma formation [Dziadzio M. et al., 2011; Moller-Quernheim J. et al., 2012].

When macrophages and epithelioid cells merge, giant cells of the original type are formed, the so-called giant cells of foreign bodies with a disordered

arrangement of nuclei, and later - cells of the Pirogov-Langhans type with an ordered peripheral arrangement of nuclei in the form of a crown [Oswald-Richter K.A. et al., 2013].

Granulomas in PS are usually smaller than those in PT and do not tend to coalesce, but may develop punctate central necrosis with accumulation of cellular debris and giant cell necrosis. More often this process is observed in the lymph nodes, clinically it is accompanied by fever, arthralgia, local redness [Binesh F. et al., 2012]. Sarcoid granulomas heal either by characteristic concentric fibrosis or by the formation of homogeneous hyaline bodies. Unlike sarcoidosis, tuberculous granulomas heal as linear or stellate scars, or lymphohistiocytic clusters remain in their place. The undulating, equally consistent course of both diseases often ends in spontaneous healing or the formation of pneumosclerosis [Cancellieri A. et al., 2013].

The most accessible, albeit insufficiently informative, method for diagnosing lung damage remains chest x-ray [Alvarez Figueroa M.V. et al., 2015].

Traditional radiological methods are important in the primary diagnosis of PS - fluorography and plain radiography of the lungs in two projections. At the same time, a symmetrical increase in the lymph nodes of the roots of the lungs and / or bilateral focal-interstitial changes in the lungs are found. An atypical X-ray picture of SL is also possible - unilateral enlargement of the intrathoracic lymph nodes (ITLN) or lymph nodes of the upper mediastinum, unilateral dissemination, foci, infiltrates, cavities, bullae.

In 10-20% of cases with PS and PT, radiographic signs in the lungs are absent at all in clinically manifested and even verified conditions (tuberculosis intoxication, zero stage of sarcoidosis). Moreover, in PT, this percentage is even higher, since lesions of the lungs with a volume of less than 2 mm are not visualized radiographically (with fluorography - less than 4 mm) [Lu Y. et al., 2017].

There is evidence that the X-ray stages of the classification of SL do not reflect the chronology of the process, it is more correct to call them “variants of

the course of the process" [Li Q.H. et al., 2012]. This became especially obvious when X-ray computed tomography (CT) became widely used in the diagnosis and monitoring of pulmonary patients [Hamzeh N., 2011; Santiago J.F.Y., 2015].

There are other methods for examining the lungs (spirometry, magnetic resonance imaging (MRI), perfusion pulmonoscintigraphy with MMA-Tc-99m, ultrasound with transesophageal fine-needle aspiration biopsy of the lymph nodes, etc.) [Soussan M. et al., 2013; Ozgul M.A. et al, 2014; Gnass M. et al., 2015; Thillai M. et al., 2017].

At the same time, the criteria for establishing the diagnosis of PS are currently: correspondence of the clinical and radiological picture; the presence of noncaseating sarcoid granulomas in the biopsy material; as well as the exclusion of the presence of bacterial, fungal and viral pathogens, primarily tuberculosis pathogens, in the studied tissues and BAL fluid [Fernandez-Sanchez M., Saeb-Lima M., 2012; Dubaniewicz A., 2018].

The analysis of literature data showed that, despite the significant replenishment of information about PT and PS, at present the problem of their differentiation and differential diagnosis has not been resolved. In preparing this review, it was noted that significantly fewer works are devoted to PS than to PT, approximately in a ratio of 1:8. This testifies to the particular relevance of the problem of tuberculosis, but the problem of PS does not lose its significance and seems to be even less studied. The unknown etiology of this disease and the controversial adequacy of most of its models limits the possibilities and resolution of the methods of its complex diagnostics.

The pathogenesis of PT and PS has been studied for a long time, but there is not enough data in the literature on the differences in indicators of hormonal status, vitamin D metabolism, the state of humoral and cellular immunity and autoimmunity, the pathogenesis of endogenous intoxication, and opinions on the degree of diagnostic information content of individual clinical, laboratory, instrumental and radiation methods. studies are also conflicting. At the same time, there are no generalizing recommendations on the rational combination of modern

diagnostic methods (including the ELI test) in the management of patients with PT and PS, and options for their treatment.

All of the above seems to be extremely important and especially relevant for modern daily practice in the dynamic monitoring of patients with PS and formed the basis for choosing the purpose and design of this study.

CHAPTER 2 MATERIALS AND RESEARCH METHODS

2.1 Clinical material

To achieve the set goals and objectives in 2011-2017. 125 male and female patients from 22 to 69 years old were comprehensively examined. Clinical material with the examination of patients with PT, PS and practically healthy people was collected in several institutions:

• in the clinic of the department of radiology with a course of ultrasound examinations of the S. M. Kirov Military Medical Academy.,

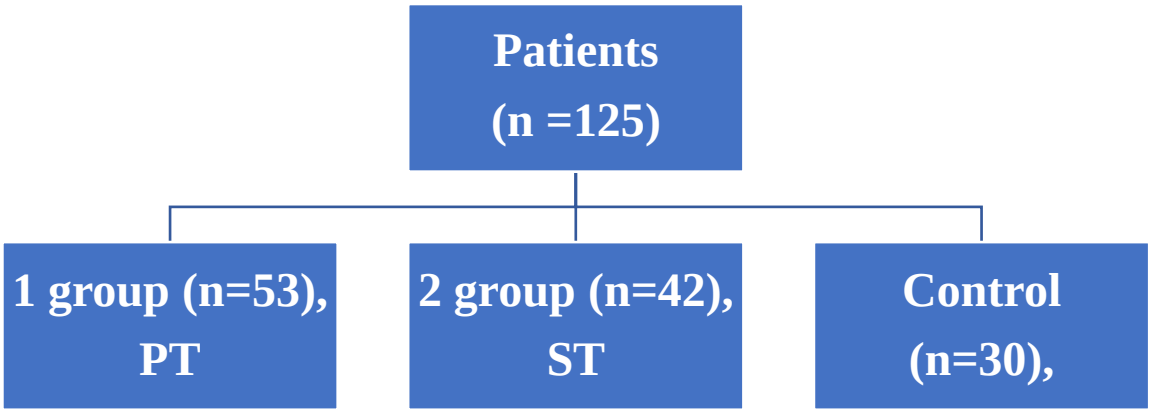
• in the Federal State Budgetary Institution "St. Petersburg Research Institute of Phthisiopulmonology of the Ministry of Health of the Russian Federation";

• in the St. Petersburg State Budgetary Institution of Health Care "City Multidisciplinary Hospital No. 2",

• in the "Center for Intensive Pulmonology and Thoracic Surgery", an observation room for patients with sarcoidosis;

• in the Federal State Budgetary Institution, tuberculosis sanatorium "Zhemchuzhina" of the Ministry of Health of the Russian Federation.

The main group consisted of 95 patients, of which: 53 people with a previously diagnosed pulmonary tuberculosis were included in the 1st group and 42 patients with a previously diagnosed pulmonary sarcoidosis were included in the 2nd group. The remaining 30 examined, practically healthy patients, made up the control group - Fig. 1 [Nikolaev A.V. et al. 2021].



Pic.1 - Study design

The criteria for inclusion of patients in the study were:

- age within 22 - 69 years;

- previously documented diagnosis of pulmonary tuberculosis (Group 1 - 53 people) and pulmonary sarcoidosis (Group 2 - 42 people).

The criteria for exclusion of patients from the study were:

-age under 22 years old and over 69 years old

- pregnancy in women; - the presence of documented alcohol, drug addiction, oncological pathology in patients;

- the presence of terminal forms of diseases. [Nikolaev A.V. et al. 2021].

2.2 Research methods

A comprehensive examination of patients was carried out using clinical, laboratory and instrumental methods in accordance with the standards, in accordance with the regulatory documents of the Ministry of Health of the Russian Federation. At the first stage, a general clinical examination of patients was carried out (collection of complaints, anamnesis, examination, analysis of the results of previously performed studies). [Nikolaev A.V. et al. 2021].

2.2.1 Laboratory research methods

In the dynamics of observation, an assessment of hematological tests was carried out in a complex way according to a clinical blood test with the calculation of indicators of the leukocyte index of intoxication (LII, normally 0.5-1.5 conventional units) according to Ya.Ya. Kalf-Kalifa (1941), modified by A.L. Kostyuchenko A.L., Sokolov (2001) and the indicator of nuclear intoxication index (NII) (Dashtayants G.A., 1978), characterizing the presence of endotoxicosis and inflammatory response of the organism.

Indicator LII Kalf-Kalif Ya.Ya. (1941), calculated by the formula:

$$LII = \frac{(4M + 3Yu + 2P + S) \times (Pl + 1)}{(L+M)x)(Eoz)}, \text{ where: } (L + M) x) (Eoz+1) \quad (1)$$

M - myelocytes, Yu - young, P - stab, C - segmented leukocytes, Pl - plasma cells, L - lymphocytes, M - monocytes, Eoz. - eosinophils (in % of the blood formula).

In the modification of A.L. Kostyuchenko and A.A. Sokolov (2001), the LII indicator is simplified, eosinophils are excluded from the calculation formula:

$$LII = \frac{0.1 \times \text{Leukocytes (thousand/µl)} \times \text{Neutrophils (\%)}}{100\text{-neutrophils (\%)}}, \quad (2)$$

The indicator of NII (Dashtayants G.A., 1978) was calculated by the formula:

$$YII = \frac{Mi+U+P}{} C, \quad (3)$$

where: Mi — myelocytes; Yu - young forms; P - stab and C - segmented leukocytes (in % of the blood formula). The norm is YII, equal to 0.05-0.08 conventional units. units [Kligunenko V.I. et al. (2004).

Liver function was assessed by a biochemical blood test (total protein, albumin, bilirubin, alanyl aminotransferase (ALT) and aspartate aminotransferase (AST), glucose, cholesterol, coagulogram). Kidney function was assessed by the level of creatinine in the blood and by the clinical analysis of urine, its inoculation, samples of Zimnitsky, Nechiporenko, as well as according to ultrasound examination (ultrasound) of the kidneys [Nikolaev A.V. et al. 2021].

When assessing the parameters of the immune system, the phagocytic function of neutrophils was determined using the cytochromatic method according to the nitroblue tetrazolium reduction reaction (NBT-test), while in relation to the induced NBT-test to the spontaneous NBT-test, the stimulation index (SI) was calculated, the value of which was used to judge the value of phagocytic activity (reserve) of neutrophils; in arbitrary units (conventional units) [Nikolaev A.V. et al. 2021].

The absolute and relative content (in %) of the main subpopulations of immunocompetent cells in peripheral blood was determined using the method of flow cytometry on a flow cytometer The relative content of lymphocytes with the phenotype CD3+ (T-lymphocytes), CD4+ (T-helpers), CD8+ (cytotoxic T-lymphocytes), CD20+ (B-lymphocytes), CD16+CD56+ (NK killer cells) (Multitest, Beckton Dickinson, USA). The CD4/CD8 ratio was also calculated for a more accurate assessment of lymphocyte function (FacsCanto II (Beckton Dickinson, USA) [Nikolaev A.V. et al. 2021].

The state of humoral immunity was assessed by the content of immunoglobulins (Ig) isotypes A, M and G, which was determined using enzyme-linked immunosorbent assay using the double antibody method with kits of reagents "ELISA-BEST" (VECTOR BEST, Russia). The concentration of circulating immune complexes (CIC) of medium and low molecular weight (SMM and nLMM, respectively) was determined by a spectrophotometric method using polyethylene glycol-6000. The reaction was evaluated on an SF-26 spectrophotometer (LOMO, Russia).

The content of cytokines - tumor necrosis factor-α (TNF-α), interferon-γ and interleukins: 2, 4, 6 (IL-2, IL-4, IL-6) in blood serum was studied using enzyme immunoassay using diagnostic tests -systems LLC "Protein contour" (Russia).

Screening assessment of the spectrum and intensity of autoimmune reactions in patients was performed using enzyme immunoassay solid-phase non-competitive semi-quantitative determination of serum autoantibodies (AAB) to 24 antigens using the ELI-Viscero-Test-24 test system (MIC Immunculus, Moscow, Russia). This test system made it possible to determine and evaluate, relative to the control pool of sera of healthy donors and relative to the own average immunoreactivity of each individual, the content of 24 AAT types to the following antigens:

- to ds-DNA (AAT to double-stranded DNA);

- to β2-glycoprotein I (AAT to the main phospholipid-binding protein of blood plasma);

- to Fc-Ig (AAT to the Fc fragment of immunoglobulin molecules, rheumatoid factors);

- to CoM-02 (AAT to the membrane antigen of myocardiocytes),

- to β1-adrenergic receptors (AAT to the isoform of adrenoreceptors of cardiomyocytes);

- to TrM-03 (AAT to platelet membrane antigen);

- to ANCA (AAT to cytoplasmic antigens of neutrophils);

- to KiM-05 (AAT to the membrane antigen of glomerular cells of the kidneys);

- to KiS-07 (AAT to the cytoplasmic antigen of the cells of the glomeruli of the kidneys);

- to LuM-02 (AAT to the membrane antigen of the cells of the epithelium of the pulmonary alveoli);

- to LuS-06 (AAT to the cytoplasmic antigen of the cells of the epithelium of the pulmonary alveoli);

- to GaM-02 (AAT to the membrane antigen of the cells of the stomach wall, an excess of antibodies is associated with degenerative changes in the stomach wall);

- ItM-07 (AAT to the membrane antigen of the cells of the wall of the small intestine);

- to HeS-08 (AAT to the cytoplasmic antigen of hepatocytes;

- to HMMP (AAT to the membrane antigen of mitochondria of hepatocytes;

- AAT to insulin;

- AAT to insulin receptors;

- AAT to thyroglobulin;

- AAT to thyroid-stimulating hormone (TSH) receptors;

- to AdrM-D/C-0 (AAT to the membrane antigen of adrenal cells);

- to Spr-06 (AAT to the membrane antigen common to prostate cells and spermatozoa);

- to S100 (AAT to calcium-binding protein S100);

- to GFAP (AAT to acid fibrillar astroglial protein);

- to MBP (AAT to myelin basic protein) [Nikolaev A.V., 2019б Nikolaev A.V. et al. 2021].

For each studied AAT, according to the manufacturer's methodology [Poletaev A.B., 2019; Poletaev AB. et al., 2007, 2020; Neamatzadeh H. et al., 2016] based on the enzyme immunoassay determination of the absolute content of AAT in arbitrary units of optical density, the following were calculated:

• percent deviation from the pool of control sera of healthy donors with the sign "+" (above the pool), with the sign "-" (below the pool).

• Average autoimmunoreactivity of an individual, representing the algebraic sum of all deviations from the control pool for each of the 24 AATs, divided by 24.

• The autoimmunological profile of an individual, representing the variations in the deviations of each of the 24 AAT types from the individual average immunoreactivity, taken as an isoline.

In addition, in patients of all groups, using a competitive enzyme-linked immunosorbent assay (ELISA) with the following sets of reagents, the serum concentrations of the following bioregulators were studied: procalcitonin, cortisol, triiodothyronine (T3), thyroxine (T4), TSH ("ELISA-BEST" Vector Best Baltica, Russia), prolactin (Monobind Inc., USA), cathelicidin (Hycult Biotech, Netherlands). 25-hydroxyvitamin D (calcifediol) and 1,25-dihydroxyvitamin D (calcitriol) (Immunodiagnostic Systems Ltd).

2.2.2 Instrumental and radiology research methods

The study of the function of external respiration was carried out using a computer spiroanalyzer "ETON 01-22" (Russia). To characterize the ventilation function of the lungs, standard indicators were used: vital capacity (VC), forced vital capacity (FVC), forced expiratory volume for the 1st second (FEV 1), FEV1 / VC ratio (Watchal-Tiffno index).

To calculate the level of impaired patency of the bronchial tree, the parameters of the forced expiratory curve were used: instantaneous exhalation volume velocity 25% FVC (ISO 25), instantaneous exhalation volume velocity 50% FVC (ISO 50) and instantaneous exhalation volume velocity 75% FVC (ISO 75). In each study, 3 or more quiet expiration attempts were selected; in the event that in the FVC mode during the study, the FVC index was greater than the VC, the attempt was repeated. During the study of forced expiration, the time to reach the peak volumetric velocity did not exceed 0.2 sec, and the time to complete the FVC maneuver did not exceed 5-6 sec, which made it possible to achieve objective results. In accordance with the recommendations of the device manufacturer, the results of the study for each indicator were divided into categories: below the norm, norm, above the norm. On the basis of the data obtained, the clinical and pathophysiological type of respiratory dysfunction was established: restrictive, obstructive, or mixed.

X-ray methods of diagnostics. Panoramic digital radiography of the chest organs was performed using the Clinomat apparatus (Italray, Italy). The study was performed in direct anteroposterior and lateral projections. The patient was in a standing position with his hands raised behind his head, while holding his breath while inhaling. The irradiation intensity was selected individually; on average, it did not exceed 0.03 mSv. For each patient, according to the results of the study, the radiologist made a conclusion according to the standard protocol. When evaluating radiographs, the following radiographic manifestations were taken into account: enlarged mediastinal lymph nodes, single large foci, ground glass syndrome, and pleural effusion.

Computed tomography of the chest organs was performed on a SOMATOM Definition AS 64 tomograph (Siemens, Germany). The patient was in the supine position, head first. The study was carried out in the direction from the head to the legs, the tomogram was frontal. The scope of the study is from the level of the jugular notch to the level of the frontal sinuses. The tomography mode is spiral. The thickness of the tomographic section was 1.5 mm, the helix pitch was 1 mm. The breath was held at the depth of inspiration, contrasting was not performed. The presence of focal formations was assessed; state of interstitial structures; the shape, structure and contours of the lymph nodes, the presence of calcifications and other signs. For each patient, according to the results of the study, the radiologist made a conclusion according to the standard protocol. Separately, the following pathological signs were taken into account: mediastinal lymphadenopathy, ground glass syndrome, single large foci, small-focal dissemination, consolidation syndrome, massive fibrosis, bronchiectasis, pleural effusion.

2.3 Statistical processing of the material

Statistical processing of the obtained data was carried out on a personal computer using STATISTICA 10 software for Windows (StatSoft, USA) and Excel (Microsoft, USA). To describe the data obtained, mean values and standard deviations were calculated in each group for all quantitative indicators. Qualitative data were expressed in terms of frequency of occurrence in %. Statistical significance of differences between the frequency indices of the groups was assessed using Pearson's $\chi 2$ test (chi-square) taking into account the Yates correction. The values of quantitative indicators were tested for compliance with the normal distribution using the Kolmogorov-Smirnov method.

To identify statistically significant differences between groups in terms of quantitative indicators, Student's parametric test was used for unrelated samples with a normal distribution of the trait. In the absence of a normal distribution of trait values, the statistical significance of differences between groups was assessed using the nonparametric Mann-Whitney U-test. The critical value of the level of statistical significance of the null hypothesis was taken equal to 0.05 [Nikolaev A.V. et al. 2021].

CHAPTER 3 RESULTS OF CLINICAL AND LABORATORY STUDIES AND THEIR DISCUSSION

3.1 Clinical characteristics of the examined patients

The review of the literature indicated that the clinic of PT and PS has many similarities, which is also confirmed by the data obtained.

A total of 53 patients with PT (Group 1), 42 with PS (Group 2), were examined, and 30 practically healthy individuals made up the control group.

The average age of study participants in the 1st, 2nd and control groups was 48.5±1.8, 52.1±1.7 and 46.7±1.6 years, respectively, and the difference between these indicators was not statistically significant. ($p>0.05$) [Nikolaev A.V. et al. 2021].

In total, among the 125 examined, there were 59 men (55.1%) and 48 women (44.9%). In the 1st group, among patients with PT, there were more men (n=32; 60.4%) than women (n=21; 39.6%; $p<0.05$). In the 2nd group with PS, women predominated (n=23; 54.8%), there were fewer men (n=19; 45.2%; $p>0.05$). In practically healthy patients in the control group, these figures were 46.7% and 53.3%, respectively ($p>0.05$) [Nikolaev A.V. et al. 2021].

Concomitant somatic pathology was detected in pulmonary patients equally often: in PT in 46 out of 53 people (86.8±4.6%), in PS in 36 out of 42 (85.7±5.0%; $p>0.05$), usually in people over 40 years of age. In the first place were diseases of the cardiovascular system (CVS): in 20.8% of patients from the 1st group and in 26.2% of patients of the 2nd group, more often in the form of arterial hypertension and coronary heart disease - Table 1.

Table 1 - The frequency of concomitant somatic diseases in patients of the 1st and 2nd groups (M ± m, %)

Comorbidities	Group 1 (n=53)		Group 2 (n =42)	
	Total	M±м %	Total	M±м %
CVS diseases	11	20,8±5,6	11	26,2±6,8
ODS diseases	9	17,0±5,2	8	19,0±6,0
RS diseases	8	15,1±4,9	7	16,7±5,8
diabetes mellitus	7	13,2±4,6	5	11,9±5,0
Liver and gastrointestinal diseases	6	11,3±4,3	7	16,7±5,8
UTI diseases	5	9,4±3,9	3	7,1±3,9
NS diseases	4	7,5±3,7	3	7,1±3,9
Pathology of the thyroid gland	3	5,7±3,3	2	4,8±3,7

Notes:1/ CVS - cardiovascular system; ODS - musculoskeletal system; RS - reproductive system; GIT - gastrointestinal tract; UTI - urinary tract; NS - nervous system; 2/ the difference in the frequency of indicators in the 1st and 2nd groups is not significant (p> 0.05) [Nikolaev A.V. et al. 2021].

The second place in frequency was occupied by diseases of the musculoskeletal system (ODS) in the form of arthritis, arthrosis of the joints of the extremities, osteochondrosis - in 17.0% of patients from the 1st group and in 19.0% - from the 2nd group. Diseases of the reproductive system (RS), such as uterine fibroids in women and benign prostatic hyperplasia in men, in general, were observed in 15.1% and 16.7% of patients of the 1st and 2nd groups, respectively [Nikolaev A .IN. et al. 2021].

Differences in the rates of concomitant somatic diseases in patients with TL (Group 1) and SL (Group 2) were not statistically significant (p>0.05).

It is characteristic that various endocrine-related pathologies (diabetes mellitus, MS and thyroid diseases) were somewhat more common in patients of the 1st group (in 17 out of 53 people - 32.1 ± 6.4%; in 1 patient combined with each other), than in the 2nd sample - in 11 out of 42 (three were in combinations) -26.2±6.8%; p>0.05) [Nikolaev A.V. et al. 2021].

The combination of PT and PS with somatic pathology aggravating the course of the underlying disease is reported by many authors [Perelman M.I., Mikhailova Yu.V., 2015; Markevitz N. et al., 2017]. Among the many risk factors for the development of bronchopulmonary pathology, smoking is known to be one of the main ones, and it is emphasized that, upon learning that they are affected by PT or PS, many patients quit smoking [Bagisheva N.V. et al., 2017; Julian M. W. et al., 2013].

This is exactly what we found when examining patients: the fact of smoking earlier in the 1st and 2nd samples was noted in every second (52.8±6.9% and 57.1±7.6%, respectively (p>0.05), but at the start of the survey, among PT patients, 17 of 53 patients smoked (32.1±6.4%; average smoking experience was 8.1±1.9 years), and in the 2nd cohort with SL, these indicators were almost the same and amounted to 29.2±9.3% and 7.2±1.6 years, respectively (p>0.05).

Thus, the average indicators of age, frequency of concomitant somatic pathology and smoking in the studied groups of patients with PT and PS were almost the same, but PT was more common (p < 0.05) in men, and PS was more common in women (p> 0.05).).

When interviewing patients, first of all, complaints from the respiratory system (cough, sputum production, shortness of breath, etc.) were recorded with an assessment of their frequency - Table 2.

It was found that complaints of cough, expectoration of sputum, chest pain, hemoptysis in patients with PT were 1.7, 3.9, 2.7 and 7.6 times more often (p<0.05) than in patients with PS. On the contrary, in PS, more often than in PT, complaints of shortness of breath were recorded (1.4 times; in 23.8±6.6% and 17.0±5.2% of patients, respectively; p>0.05), some had attacks of suffocation

(4.2%), with PT there were no such attacks in any of the observations. With PS, there have never been complaints of hemoptysis [Nikolaev A.V. et al. 2021].

Table 2 - Frequency and nature of "pulmonary" complaints in patients with tuberculosis and pulmonary sarcoidosis (M±m%).

Complaints	Group 1 (n=53)		Group 2 (n=42)	
	Total	M±м%	Total	M±м%
Cough	24	45,3±6,8	12	28,6±7,0
Sputum production	10	18,9±5,4	2	4,8±3,4*
Dyspnea	9	17,0±5,2	10	23,8±6,6
Chest pain	10	18,9±5,4	3	7,1±3,9
Hemoptysis	4	7,6±3,7	-	0,0±0,0
Asphyxiation	-	0,0±0,0	2	4,8±3,4

Note: * - the results in the frequency of indicators are statistically significant ($p<0.05$).

The results of the analysis of general complaints and symptoms (weakness, malaise, fever, weight loss, arthralgia, myalgia, erythema nodosum, complete Löfgren's syndrome) in patients with PT and PS are presented in Table 3 [Nikolaev A.V. et al. 2021].

Table 3 - Frequency of "non-pulmonary" complaints and symptoms in patients of the 1st and 2nd groups (M ± m %)

Complaints	Group 1 (n=53)		Group 2 (n=42)	
	Total	M±м%	Total	M±м%
Weakness, malaise	16	30,2±6,3	18	42,9±7,6
Increase in body temperature	18	34,0±6,5	14	33,3±7,3
Irritability	17	32,0±6,4	14	33,3±7,3
Sleep disturbance	18	34,0±6,5	14	33,3±7,3
Weight loss	6	11,3±4,3	2	4,8±3,4
Arthralgia	2	3,8±2,7	12	28,6±7,0*
Myalgia	-	0,0±0,0	2	4,8±3,4
Erythema nodosum	-	0,0±0,0	3	7,1±3,9
Complete Löfgren's syndrome	-	0,0±0,0	3	7,1±3,9

Note: * - the difference in indicators in the 1st and 2nd groups of patients is significant ($p<0.001$).

The difference in the frequency of these manifestations was statistically significant only in relation to arthralgias: in PS they were noted in 28.6±7.0% of patients, which was 7.5 times more common than in PT - in 3.8±2.7 % of patients ($p < 0.001$).

However, in both the 1st and 2nd samples of patients, a relatively high frequency of complaints of weakness, malaise (in 30.2±6.3% and 42.9±7.6%, respectively; $p> 0.05$), every third in the groups had an increase in body temperature, irritability, sleep disturbance ($p> 0.05$) [Nikolaev A.V. et al. 2021].

In patients with PT, 2.4 times more often than with PS, there was a loss of body weight (in 11.3±4.3% and 4.8±3.4%, respectively; $p>0.05$) and never detected complaints of myalgia, erythema nodosum and the presence of complete Löfgren's syndrome. At the same time, in the group of patients with SL, these manifestations were observed in 4.8%, 7.1%, and 7.1% of cases, respectively ($p>0.05$).

Thus, among the conditionally “extrapulmonary” complaints and symptoms of patients with PT and PS, in every third case there were complaints that indirectly indicated the syndrome of excessive systemic action of inflammatory mediators (autacoids) - ISDA (“general intoxication”): weakness and malaise (in PS - in 41.7%), fever, irritability, sleep disturbance. Moreover, these complaints were usually combined with each other, intensified during exacerbations. Less commonly, in PT and PS, complaints of weight loss were noted (in PT more often by 2.4 times: $p>0.05$). Patients with PT are not characterized by arthralgia (they were 7.5 times more common in PS), and myalgia, erythema nodosum, and complete Löfgren's syndrome were not encountered at all, which were noted in 4.8%, 7.1%, and 7.1% in PS. observations, respectively [Nikolaev A.V. et al. 2020].

3.2 Hematological studies of patients with sarcoidosis and pulmonary tuberculosis

Hematological comprehensive laboratory blood tests in patients with PT and PS were as follows. Note that the above symptoms are most typical for rheumatological diseases, which are known to be of an autoimmune and immunopathological nature.

3.2.1 Clinical blood test data

The average indicators of the state of "red" blood (the number of erythrocytes, hemoglobin level and hematocrit), as well as the number of platelets in patients with TP and PS were statistically significantly lower (to a greater extent in the 1st group) than in healthy people in the control group ($p<0.05$) – tab. 4.

At the same time, in comparison with the data in the control group, patients with PT (to a greater extent) and PS showed a significant increase in the average values of the number of leukocytes, the percentage of stab neutrophils and lymphocytes ($p<0.05$). In general, with pulmonary pathology, patients had tendencies to anemia and an increase in the response of the acute phase in the body, more pronounced in PT, but the difference in indicators in the 1st and 2nd groups was not statistically significant ($p> 0.05$) [Nikolaev A.V. et al. 2020].

Table 4 - Indicators of the general clinical analysis of blood in the examined patients (M ± m)

Indicators	Group 1 (PT; n=53)	Group 2 (PS; n=42)	Control (n=30)
Erythrocytes, x1012/l	4,1±0,07*	4,3±0,1*	4,9±0,07
Hemoglobin, g/l	112,4±5,3*	122,4±4,2*	142,9±2,4
Hematocrit,%	40,9±0,2*	41,3±0,2*	42,5±0,3
Reticulocytes,%	1,5±0,2	1,5±0,1	1,5±0,1

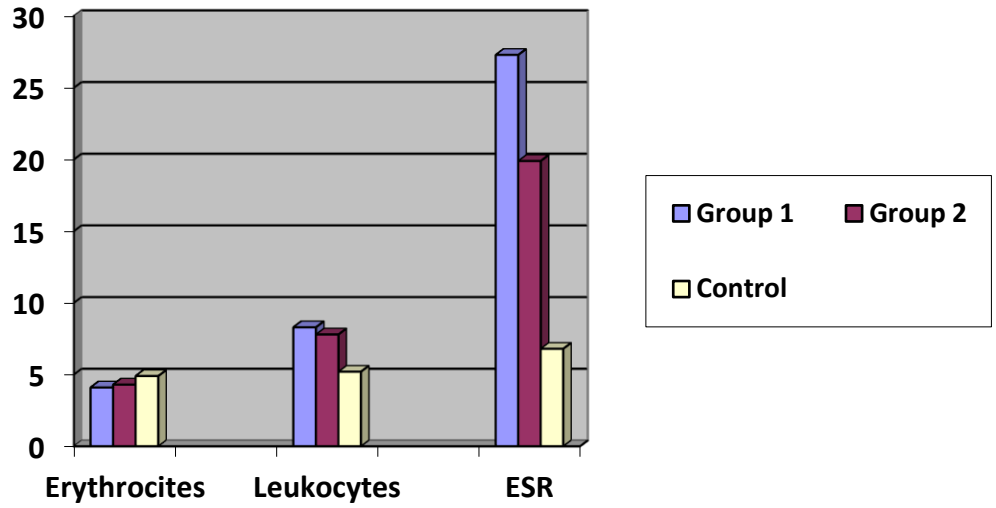
Continuation of Table 4			
Indicators	Group 1	Group 2	Control (n=30)
Platelets, x109/l	208,2±7,0*	219,4±6,1*	272,4±8,6
Leukocytes x109/l	8,3±0,3*	7,8±0,3*	5,2±0,3
ESR, mm/h	27,3±1,4*	19,6±1,7*#	6,8±1,4
Basophils,%	0,4±0,05	0,3±0,06	0,3±0,03
Eosinophils,%	3,0±0,2*	2,5±0,2*	1,1±0,3
Neutrophils p / I,%	4,3±0,4*	3,6±0,3*	1,3±0,2
Neutrophils s / i,%	50,8±2,5*	51,9,±2,8*	60,9±1,3
Lymphocytes,%	34,4±0,4*	35,8±0,5*	31,2±0,3
Monocytes,%	7,1±0,5*	5,9±0,3	5,2±0,3

Notes: *- differences in indicators in the 1st and 2nd groups are significant relative to the indicators of the control group ($p<0.05$-0.001);

- differences between the indicators of the 1st and 2nd groups are significant ($p<0.05$).

Only in the average ESR in the groups of patients with PT and PS were there significant differences (27.3±1.4 mm/h and 19.6±1.7 mm/h, respectively; $p<0.01$) and in both groups of patients the rate was higher than that of healthy patients with a high degree of statistical significance (6.8±1.4 mm/h; $p<0.001$).

Thus, in the main quantitative indicators of the clinical blood test in PT and PS, in comparison with the data in healthy patients, the same unfavorable trend was noted: a decrease in the number of erythrocytes (in millions), an increase in the number of leukocytes (in thousands) and an ESR index (mm/hour), especially at TPL- pic. 2.



Pic. 2 - Average indicators of the number of erythrocytes (million), leukocytes (thousand) and ESR (mm/hour) in the examined patients

But it should be noted that, in general, most of the main average hematological indicators (except for the ESR indicator) did not go beyond normal intervals, remaining either at their upper limit (leukocyte count) or at the lower limit (hemoglobin indicator). This fact is due to the fact that the majority of patients were examined at the stage of compensation for PT and PS diseases. During exacerbations of the disease, the analyzes worsened, which manifested itself in the form of a decrease in the values of red blood indicators, an increase in leukocytosis, a shift of the leukocyte formula to the left and an acceleration of ESR, which confirmed the presence in patients with PT and PS of not only progressive anemia, but systemic correlates of inflammation, which could be caused by suggest the presence of the ISDA syndrome - excessive systemic action of autacoids of a pro-inflammatory nature.

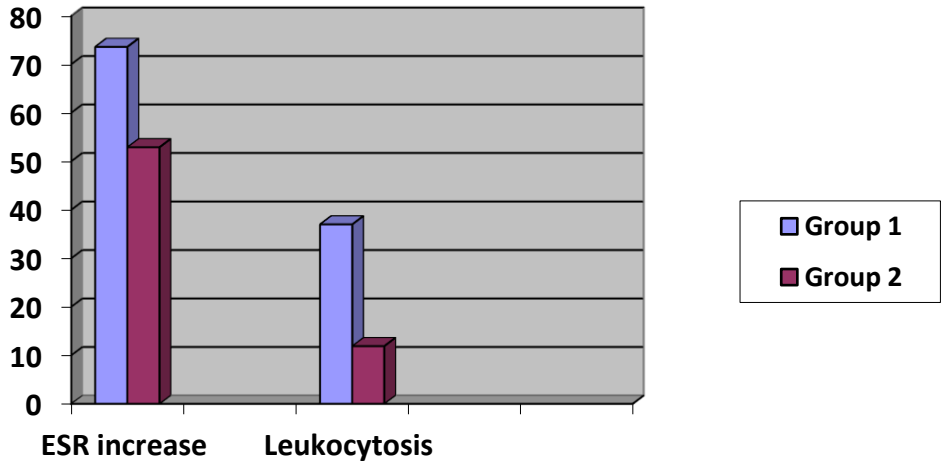
To clarify the severity of the acute-phase and inflammatory response of the body in the 1st and 2nd groups of patients, according to a clinical blood test, the frequency of an increase in ESR of more than 15 mm/h and leukocytosis of more than 8 thousand/μl was studied (table 5).

Table 5 - Identification of individual pathological changes in the clinical blood test (M±m%)

Indicators	Group 1 (PT; n=53)		Group 2 (PS; n=42)	
	Total	M±м%	Total	M±м%
ESR increase >15 mm/h	39	73,6±6,1	22	52,3±7,7*
Leukocytosis > 8 thousand/µl	18	37,0±6,6	5	11,9±5,0*

Note: *- differences in indicators in the 1st and 2nd groups are significant ($p<0.05$).

The ESR indicator turned out to be more informative, the increase of which was more often noted in the group of patients with PT (in 73.6±6.1%) than in PS (52.3±7.7%; $p<0.05$). Leukocytosis was observed less frequently than elevated ESR - in PT and PS it occurred in 37.0±6.6% and in 11.9±5.0% ($p<0.05$) of observations, respectively - Fig. 3.



Pic. 3 - The average frequency of increased ESR is above 15 mm/h, leukocytosis is more than 8 thousand/µl in patients with PT and PS.

Such changes in homeostasis are typical for various disorders of the natural detoxification system (NED) with excessive systemic action of autakoids (ISDA syndrome), as a result of the accumulation of endogenous toxic substances (ETS). The lungs are known to take an active part in SED, in particular, oxidizing

xenobiotics and neutralizing autacoids [Philpot RM, Smith BR. 1984; Churilov L.P., 2021].

The increase in ESR is associated with the acute phase response and the systemic, as well as hepatotropic effect of pro-inflammatory cytokines on blood cells and plasma proteinogram [Churilov L.P., 2021]. From the point of view of ideas about endotoxicosis (as the systemic action of inflammatory autacoids was traditionally called in the early period of the development of pathophysiological ideas about it), the acceleration of ESR is interpreted as reflecting the level of loading of erythrocyte membrane receptors with endogenous autacoid substances that contribute to the aggregation of blood cells, their destruction in capillaries with progressive disorders microcirculation and anemia, followed by hemic hypoxia, accumulation of underoxidized toxic substances in the body [Malakhova M.Ya., 2000]. The author emphasized that in severe endotoxicosis (ISDA syndrome), the ESR may decrease to 10 mm/h and below, which indirectly indicates the absence of erythrocyte glycocalyx (destruction) and the inability of cells to further adsorb the mentioned molecules on their surface. This is the so-called "paradoxical phase" of endotoxicosis (ISDA syndrome), characterized by a simultaneous increase in the content of endogenous toxic substances (ETS; autacoids) in the blood plasma, since erythrocytes lose the ability to bind them. Cells become more and more “rigid”, low-plasticity, preventing blood flow in microvessels, and, hence, oxygenation, tissue nutrition, with an increase in filtration pressure in the capillaries [Kostyuchenko A. L., Sokolov A. A., 2001].

In the decompensation phase of the endogenous intoxication syndrome (SEI, in the current interpretation - ISDA), altered cells (echinocytes, destroyed cell fragments - schistocytes) with polychromasia appear in blood smears, indicating accelerated toxic intravascular hemolysis of cells. At the same time, a reliable assessment of the severity of endotoxicosis (ISDA) is possible only when studying the indicators of membrane permeability, the sorption capacity of erythrocytes, which change for the better only during detoxification therapy [Vyugov M.A., 2018].

N.A. Negovsky et al (1987) emphasized that the number of red cells in the vascular bed decreases not only as a result of hemolysis, but also due to the deposition of ETS-loaded erythrocytes in the liver. Moreover, in a critical pre-shock state with venous congestion in the abdominal viscera, up to 40% of the total number of erythrocytes can be deposited in the liver.

The presence of the ISDA syndrome can be confirmed by the calculated indicators of the leukocyte and nuclear indices of intoxication (LII and NII, respectively - see Chapter 2).

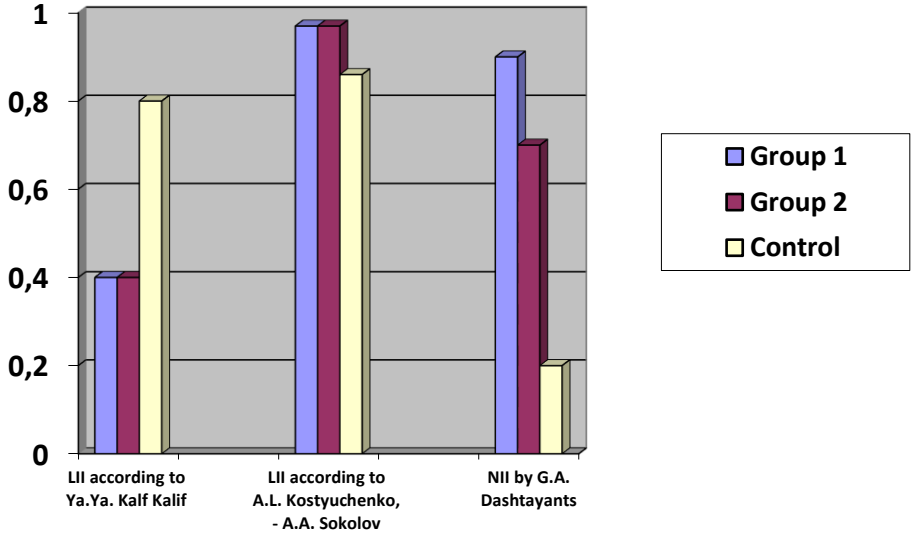
In comparison with the data of the control group, the average indicators of LII according to Kalf-Kalif in the 1st and 2nd groups turned out to be significantly two times lower (in PT and PS they were the same, 0.4±0.02 c.u. each) due to the presence of eosinophils in the blood test, and the indicators of LII according to Kostyuchenko-Sokolov corresponded to the clinical data in patients of both groups, were significantly higher (in PT and PS they were the same, 0.97 ± 0.03 units each) and significantly higher than in healthy patients (0.86±0.04; 0<0.05) - table 6.

Table 6 - Average indicators of leukocyte and nuclear indices of intoxication (M ± m)

Indicators.	Group 1 (PT; n=53)	Group 2 (PS; n=42)	Control (n=30)
LII according to Ya.Ya. Kalf Kalif	0,4±0,02*	0,4±0,02*	0,8±0,04
LII according to A.L. Kostyuchenko, - A.A. Sokolov	0,97±0,03*	0,97±0,03*	0,86±0,04
NII by G.A. Dashtayants	0,09±0,003*	0,07±0,003* #	0,02±0,005

Note: 1/ * - the difference in indicators in the 1st and 2nd groups of patients is significant with the indicators in the control (p<0.05); 2/ # - the difference between the indicators in the groups of patients is significant (p<0.05).

The average values of the NII index (calculated according to Dashtayants G.A., 1978) in the 1st, 2nd and control groups were 0.090±0.003 units, 0.070±0.003 units and 0.020±0.005 units, respectively. That is, like the LII indicator according to Kostyuchenko-Sokolov, the NII indicator in both groups of pulmonary patients was significantly higher ($p<0.05$) than in the control, but in the groups of patients the LII indicator was the same, and the NII indicator was significantly ($p<0.05$) is higher in PT than in PS - Pic. 4.



Pic. 4 - Mean indicators of LII according to Kalf-Kalif, Kostyuchenko-Sokolov and NII according to Dashtayants in PT, PS and in practically healthy individuals (for clarity, the absolute values are increased by 10 times)

Therefore, in comparison with LII indicators (calf-Kalif calculation gave a false-negative result), the NII indicator more accurately confirmed the presence of the ISDA syndrome (endotoxicosis) in the 1st and 2nd groups of patients and was higher in PT than in PS.

Thus, it was found that pulmonary patients had anemia and manifestations of the acute phase response, which progressed with exacerbations of PT and PS and were more pronounced with PT. The background and cause of these changes was the ISDA syndrome, confirmed by LII indicators according to Kostyuchenko-

Sokolov. At the same time, the most informative for assessing the reaction of inflammation and ISDA syndrome in PT and PS were the indicators of ESR, leukocytosis more than 8 thousand/μl and NII, which were significantly more changed in PT.

3.2.2 Biochemical indicators of blood

When studying biochemical blood tests, the same pattern was noted as when comparing its clinical analyzes: the average values of indicators in groups of patients with PT and PS were within the reference values of the norm, but were significantly closer to its boundaries than in healthy individuals in the control group ($p<0.05$-0.001; in terms of blood glucose level, the difference was not significant). Among patients with pulmonary granulomatosis, the indicators of patients with PT were farther from the parameters of the control group, but the differences were statistically significant only in the level of C-reactive protein ($p<0.05$), which in patients with PT (5.7±0.06 ng/ml) was at the upper limit of normal (0-5 ng / ml) - table 7.

Table 7 - Average values of biochemical blood analysis in patients of the 1st and 2nd groups (M±m)

Indicators	Group 1 (PT; n=53)	Group 2 (PS; n=42)	Control (n=30)
Total protein, г/л	62,4±0,9*	63,6±1,0*	74,1±1,1
Albumin, g/l	34,2±0,6*	35,5±0,4*	41,9±0,5
A/G coefficient, u.e.	1,27±0,0*	1,26±0,05*	1,30±0,04
Bilirubin, μmol/l	11,2±0,7*	10,2±0,4*	8,4±0,6

Continuation of table 7			
Indicators	Group 1 (PT; n=53)	Group 2 (PS; n=42)	Control (n=30)
Cholesterol, mmol/l	7,3±0,5 *	7,2±0,4*	6,0±0,3
ALT, units/l	30,2±0,6*	28,4±0,7*	16±0,4
AST, units/l	27,1±0,6 *	25,3±0,8*	12,4±0,6
Creatinine, mmol/l	0,07±0,004*	0,06±0,003*	0,05±0,003
Glucose, mmol/l	5,4±0,5	4,9±0,6	4,1±0,5
C-reactive protein, ng/ml	5,7±0,06*	4,5±0,04*#	1,7±0,06

Notes: 1/ *- differences in indicators in the 1st and 2nd groups are significant relative to the indicators of the control group ($p<0.05$-0.001); 2/ # - differences between the indicators of the 1st and 2nd groups are significant ($p<0.05$-0.01). T

Thus, according to the results of a biochemical blood test, it was found that, despite the presence of severe lung pathology and manifestations of ISDA, the homeostatic functions of the liver and kidneys in PT and PS were relatively preserved; The studied biochemical parameters had no diagnostic significance in PT and PS in the compensated state, except for the level of C-reactive protein.

3.3 Comparative characteristics of the immune status in patients with tuberculosis and lung sarcoidosis

Most of the average hemogram and biochemical blood tests in were worse than in healthy individuals in the control group, but within the normal range, which, apparently, reflected the relatively compensated state of the patient's body. At the same time, the body's protective inflammatory response to damaging factors is largely due to the state of one of the main bioregulatory components of this protection - the immune system.

Innate immunity (paleoimmunity) is closely related to phagocytosis.

Normally, the number of main phagocytic microphages (neutrophils) is about 10-15% of their total number, and they are in a passive state, but when exposed to any pathogen recognized by the receptors of the paleoimmunity system, energy metabolism sharply increases in an activated cell, heat production increases. and oxygen radicals are formed, moreover, components are detected that are absent (or almost absent) in the neutrophil, which is in a calm state [Churilov L.P., 2021]. At the same time, under the influence of superoxide anion (it is formed in the NADP-H-oxidase reaction and is intended to destroy the infectious agent after it is absorbed by the cell or during exocytosis), nitrosine tetrazolium (NBT) of the cell is restored to insoluble diformazan, which, in the form of granules, is deposited inside or on cell surface and its quantity serves as a criterion for the intensity of the reaction and the ability of neutrophils to destroy pathogens, which usually increases normally.

Our studies (Table 8) showed the regular dynamics of some indicators characterizing phagocytosis and innate immunity in patients with PT and PS.

In healthy people, the mean values of spontaneous and stimulated NBT tests were 12.4±1.2% and 21.1±1.3%, respectively ($p<0.001$), with PT - 20.7±1.5% and 25. 2±1.4%, respectively ($p<0.05$), with PS - 19.6±1.6% and 27.1±1.3%, respectively ($p<0.001$). That is, in both PT and PS, the indicator of the spontaneous NBT test was higher than in the control group. The difference, in comparison with the initial level, with PT was 4.5%, to an even greater extent, the indicator increased with PS - by 7.5% [Nikolaev A.V. et al. 2020].

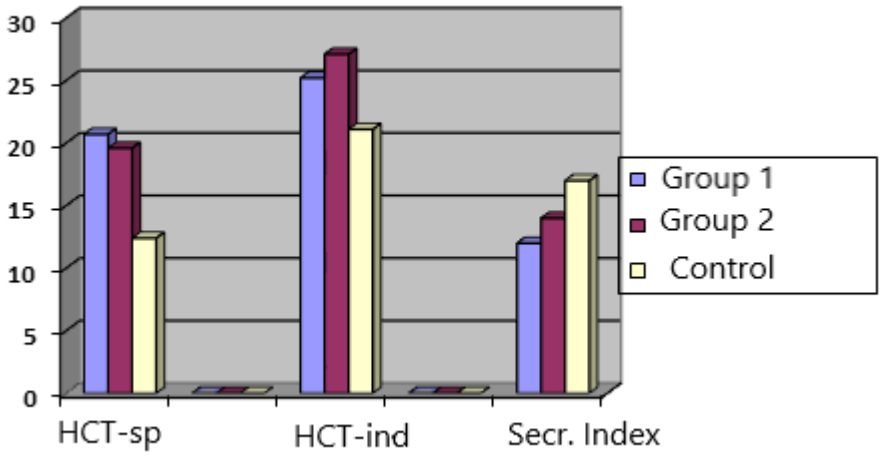
Table 8 - Indicators of nonspecific resistance and phagocytosis in the examined patients with LT, SL and in the control group (M±m%)

Indicators	Group 1 (PT; n=53)	Group 2 (PS; n=42)	Control (n=30)
NST-spontaneous,%	20,7±1,5*	19,6±1,6*	12,4±1,2

Continuation of table 8			
Indicators	Group 1 (PT; n=53)	Group 2 (PS; n=42)	Control (n=30)
NST-induced,%	25,2±1,4*	27,1±1,3*	21,1±1,3
secretion index, conv. units	1,2±0,04*	1,4±0,05*#	1,7±0,06

Notes: 1/ *- differences in indicators in the 1st and 2nd groups are significant relative to the indicators of the control group ($p<0.05$); 2/ # - differences between the indicators of the 1st and 2nd groups are significant ($p<0.05$) [Nikolaev A.V., Churilov L.P., 2020].

The average stimulation index (the ratio of stimulated to spontaneous NBT-test) in healthy people was 1.70±0.06 units, with PT - 1.20±0.04 units. units, and with PS - 1.40 ± 0.05 arb. units; ($p<0.05$). At the same time, in the groups of patients, the difference in the average values of spontaneous and induced NST was not statistically significant ($p>0.05$), and in terms of SI, it turned out to be significant ($p<0.05$) - fig. 5 [Nikolaev A.V. et al. 2020].



Pic 5 - Indicators of the NBT-test (in %%) and the secretion index (conventional units - for clarity in all groups are increased by 10 times) in the examined patients.

It is known that the spontaneous indicator of the NBT-test increases with acute intoxication and inflammation in the body (in the modern interpretation - with ISAD syndrome), in particular, with pulmonary pathology, with cancer, and SI, which reflects the functional reserves of neutrophils for the digestion of pathogens, either increases (if the resources of phagocytic leukocytes allow it), or progressively decreases with decompensation of the function of phagocytes [Nikolaev A.V. et al. 2021; Shirokhova N.M. et al., 2011]. Our studies have confirmed these statements and indicate that in both PT and PS, in comparison with healthy people, as a result of exposure to autacoids, innate immunity is activated, but the reserves of neutrophil function for destruction of pathogens in both granulomatous lung diseases are reduced, and , to a greater extent the latter is characteristic of PT. Table 5 above indicates that the average content of lymphocytes in PT and PS was almost the same, amounting to 34.4±0.4% and 35.8±0.6%, but it turned out to be significantly higher than in practically healthy people (31, 2±0.3% ($p<0.05$), which confirmed the strengthening of adaptive immunity processes in pulmonary pathology [Nikolaev A.V. et al. 2020].

Normally, the number of lymphocytes in the peripheral blood is 2% of the total number of cells of the lymphoid line in the body, and the remaining 98% are in the central (bone marrow and thymus) and peripheral (spleen, lymph nodes and non-encapsulated lymphoid tissue of the mucous membranes) organs immune system. In inflammatory processes, part of the lymphocytes migrates into the bloodstream and the affected organs, with a change in phenotypes, depending on the nature of the pathological process and the course of compensatory-adaptive reactions [Nikolaev A.V. et al. 2021; Oswald-Richter K.A. et al., 2013].

We studied the absolute and relative content of lymphocytes in the blood, and these indicators had unidirectional dynamics. Therefore, Table 9 presents only quantitative data on the relative average content (%) of immunocompetent lymphocytes in patients with PT and PS.

The relative average content of CD3+ T-lymphocytes in the peripheral blood in the 1st, 2nd groups of patients and in the control group was 74.6±7.3%,

79.1±3.6% and 74.2±8, respectively. 5%, that is, slightly increased in pulmonary pathology, especially in PS, but these changes were not statistically significant - $p>0.05$.

The indicators of the relative average content of CD20+ B-lymphocytes in PT and PS were almost the same (12.8±0.4%, 12.7±0.4%, respectively), but significantly higher than in healthy individuals - 11.7±0 .3% ($p<0.05$).

The indicators of the average relative content of T-helpers (CD4+,%) in PT and PS were almost the same (31.9±1.6% 32.2±1.4%, respectively; $p>0.05$) and significantly less in both groups than in healthy people 37.2±1.7% $p<0.05$).

According to I.Yu. Nikitina (2013), deficiency of CD4+ lymphocytes in PT leads to a worsening of the course of the disease due to insufficient production of IFN-γ with a decrease in macrophage activation against MBT. Under antigenic load, naive CD4+ lymphocytes recognize the antigen, then differentiate in the lymph nodes with the formation of effector forms of lymphocytes with special properties. Moreover, the more severe the infection and the more pronounced ISDA, the lower the CD4+/CD8+ ratio in the peripheral blood [Kojima K. et al., 2012].

This is exactly what was found in this study when assessing lymphocytograms - a decrease in the content of CD4+ in PT and PS (their proportion in PT in peripheral blood was lower than in PS and in healthy patients - see above) and a simultaneous increase ($p<0.05$) CD8+ content, in comparison with data in PS and in healthy people: the indicator was 20.4±1.8%, 15.9±1.1% and 15.3±1.0%, respectively.

At the same time, the calculated average CD4 / CD8 index, c.u. in the group of patients with PT was the lowest, amounted to 1.6 ± 0.2 c.u. and significantly differed from the index in SL - 2.0 ± 0.1 c.u. units and from that in healthy people - 2.4±0.2 units ($p<0.05$).

The percentage of natural killers (NK cells) CD16+CD56+ in peripheral blood in the 1st and 2nd groups of patients was 13.4±0.8% and 11.0±0.9%,

respectively, which was significantly higher ($p<0.05$) than in the control group (9.3±1.0 x103/μl).

Table 9 - The content of various immunocompetent cells in the peripheral blood of patients with tuberculosis and sarcoidosis of the lungs (M ± m,%)

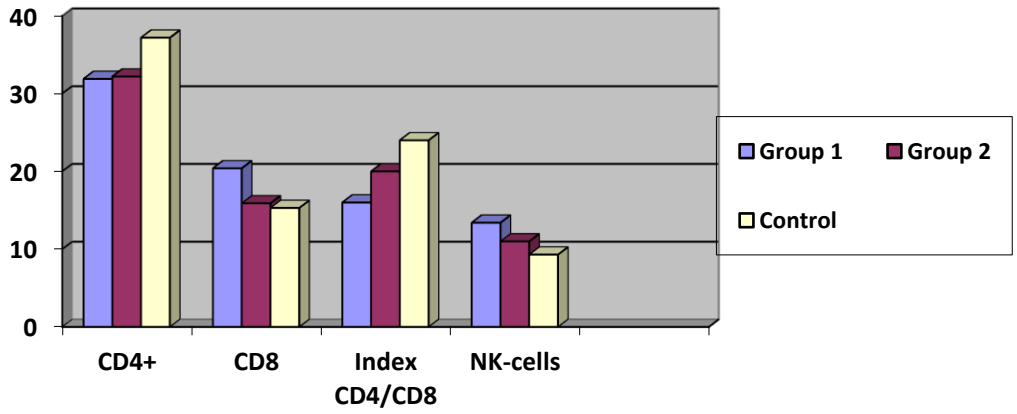
Indicators	Group 1 (PT; n=53)	Group 2 (PS; n=42)	Control (n=30)
CD3+, %	74,6±7,3	79,1±3,6	74,2±8,5
CD20+,B-cells, %	12,8±0,4*	12,7±0,4*	11,7±0,3
CD4+, helpers, %	31,9±1,6%*	32,2±1,4%*	37,2±1,7%
CD8+, supressors,% cytotoxic-T-limphocytes	20,4±1,8*	15,9±1,1*#	15,3±1,0
Index CD4	1,6±0,2*	2,0±0,1*	2,4±0,2
CD16+CD56+, effectors,% NK-cells	13,4±0,8*	11,0±0,9*#	9,3±1,0

Note: 1/* - differences in indicators in the 1st and 2nd groups are significant in comparison with the data of the control group ($p<0.05$)

2/ # - differences in indicators are significant between the 1st and 2nd groups ($p<0.05$).

It is known from the literature that an increase in the content of T-killers in the blood, as well as B-lymphocytes (CD20+) with a decrease in the CD4+/CD8+ index, occurs with increased tissue destruction, an increase in the degree of ISDA and activation of the acute phase response against the background of the inflammatory process in the body (Neimark I. I. et al., 2000; Rakhmatullina I. R. and Valieva N. G., 2003; Churilov L. P., 2021). This is what we found in

pulmonary patients, and to a greater extent these changes characterized PT: the proportion of circulating CD4+ T-lymphocytes decreased with an increase in the percentage of cytotoxic (CD8+) lymphoid cells and natural killers (CD16+CD56+,NK cells), which led to a decrease in index CD4/CD8 - fig. 6 [Nikolaev A.V. et al. 2021].



Pic. 6 - Relative content (%) in the blood of the examined persons of CD4+, CD8+, NK-cells and CD4/CD8 index (arbitrary units; for clarity, the index is everywhere increased by 10 times). Note: the 1st group, the 2nd group and the control group are marked with bars.

So, there were signs of activation of the mechanisms of cellular immunity in PT and PS. But activated lymphoid cells just secrete many of those autacoids, the excess of the systemic action of which (ISDA) was evidenced by the signs of the acute phase response described above. First of all, these are regulators of the immune response and communication factors of immunocompetent and somatic cells - cytokines that coordinate proliferation, differentiation, functioning, and degradation of cells. Being markers of the functional state of immunity, cytokines trigger various types of immune response in chronic diseases, including PT and SL [Nikolaev A.V. et al. 2021; Hyldgaard C. et al., 2012]. At the same time, it is worth emphasizing that cytokines are, by their nature, primarily local and zonal physiological regulators of short-range action. Their systemic concentrations are normally very low, but in pathology, increasing more and more, they can, to one degree or another, interfere with the neuroendocrine regulation of systemic

functions. At the same time, in fact, the response of the acute phase corresponds to a moderate ISDA, and with an extreme increase in their systemic concentrations, known as a cytokine storm, a pre-shock state occurs (systemic inflammatory response syndrome), and then a toxic-septic shock [Churilov L.P., 2021]. These stages of ISDA growth can be considered the pathophysiological equivalent of the classical concept of clinical medicine about progressive "endotoxicosis" or "general intoxication" [Nasonkin O.S., Churilov L.P., 2021].

When studying the level of cytokines in the blood of patients with PT and PS, it turned out that the concentrations of IL-2 were significantly reduced ($p<0.05$), compared with those found in the control group (98.5±6.4 pg/ml), as in PT (38.8±7.9 pg/ml) and in PS (46.2±11.2 pg/ml; $p>0.05$ with the PT group) – Table 10.

Since IL-2 is a key cytokine that promotes the differentiation of naive T-helper cells along the Th1 and Th2 pathways, it can be assumed that these processes were impaired in both granulomatosis. At the same time, the role of IL-2 is known as an inducer of the formation of T-regulators and a deterrent to the differentiation of Th17-lymphocytes, that is, the main participants in autoimmune processes [Abbas A.K. et al., 2019]. Therefore, a decrease in the concentration of IL-2 could be one of the factors for enhancing the autoreactivity of the immune system of patients, both in PT and PS (see below).

Conversely, IL-4 concentrations were significantly ($p<0.05$) increased in both PT and PS compared with the corresponding indicator in the control group (there was no significant difference between the groups of patients, $p>0.05$). At the same time, the average values of this indicator were 32.9±9.2 pg/ml in LT, 41.3±7.2 pg/ml in PS, and only 4.2±0.8 pg/ml in healthy people.

IL-4 is known as an inducer of the Th2 pathway of differentiation of CD4+ T-lymphocytes, which promotes the differentiation of plasma cells and the synthesis of antibodies, especially reagin antibodies, but suppresses the production of Th1-lymphocytes, participants in autoimmune cellular reactions, as well as the production of IFN-y. It enhances the expression of MHC type II

antigens by various cells [Abbas A.K. et al. 2019]. An increase in its level in PT and PS, in our opinion, is unfavorable and can interfere with the protective interferon response, promoting a humoral response through the pathways of anaphylactic reactions and antibody-dependent autorecognition. In addition, IL-4, as a factor that induces the M2 pathway of macrophage polarization, contributes to the attenuation of an acute inflammatory process and, especially, the development of fibroplasia [Aster J. et al., 2009]. Apparently, the changes we noted in PT reflected the fibrous-cavernous stage of the process, while in PS, for which, as noted above, M2-polarization of macrophages is typical, the increase in the concentration of IL-4 could be associated precisely with the peculiarities of the fate of macrophages during the formation sarcoid granulomas [Nikolaev A.V. et al. 2021].

Table 10 - Concentrations of cytokines in the blood plasma of the examined patients (M±m, ng/ml).

Indicators	Group 1 (PT; n=53)	Group 2 (PS; n=42)	Control (n=30)
Il-2	38,8±7,9*	46,2±11,2*	98,5±6,4
Il -4	32,9±9,2*	41,3±7,2*	4,2±0,8
Il -6	6,0±1,3*	18,7±3,8*#	3,1 ±0,4
TNF-α	114,2±11,3*	101,2±12,5*	4,3±1,2
TNF -γ	185,4±21,2*	146,7±11,3*#	50,9±1,6

Notes: 1/* - differences in indicators in the 1st and 2nd groups are significant relative to the indicators of the control group; 2/ # - differences in indicators between the 1st and 2nd groups are significant ($p<0.05$-0.001).

The content of IL-6 in the blood plasma was significantly higher in patients with PT, relative to the level of the group of patients with PS, the average values

were 18.7±3.8 pg/ml and 6.0±1.3 pg/ml (p<0, 05), respectively, and in both granulomatosis they were higher than in healthy people (3.1 ± 0.4 pg/ml; p<0.05) by 1.9 and 5.7 times, respectively. IL-6 is a powerful pro-inflammatory regulator and one of the key mediators of the acute phase response involved in ISDA at all stages, from mild to severe cytokine storm and toxic-septic shock [Abbas A.K. et al. 2019], and apparently, these figures correlated with the clinical and laboratory signs of ISDA described above in patients with PL and, to an even greater extent, with PT. At the same time, it is important that it is IL-6 that prevents the formation and function of the main cells inhibiting autoimmunity within the physiological limits - T-regulators and promotes the Th17 pathway of lymphocyte polarization associated with pathological autoimmunity [Schinnerling K, et al., 2017]. The features of the cytokine spectrum revealed by us in PT and PS could cause the development of autoimmune manifestations in these granulomatosis.

Activation of cellular immunity and ISDA was expressed in a sharp increase in the systemic concentration of one of the most important mediators of "endotoxicosis" and cellular cytotoxicity - TNF-α, the average blood levels of which in patients with PT were slightly higher than in the group of patients with PS, the average values of the indicator were 114 .2±11.3 pg/ml and 101.2±12.5 pg/ml (p<0.05), respectively. At the same time, in both groups of patients with granulomatous diseases, the concentrations of TNF-α in the blood plasma were much higher than the norm: respectively, 27 (PT) and 24 (PS) times higher than in the control group - 4.3 ± 1.2 pg / ml (p<0.001). It is appropriate to note that it is TNF-α that is considered the main signal that controls the formation of granulomas, has a clear protective effect in PT, activating innate immunity cells, and under the influence of antibodies to it, experimental tuberculosis in rodents is severe and without an effective barrier granulomatous process [Churilov L. P., 2021]. Iatrogenic use of immunotherapeutic monoclonal antibodies to this cytokine helps with a number of autoimmune and autoinflammatory diseases, including acute sarcoidosis Lofgren's syndrome, but, on the contrary, exacerbates and worsens the course of tuberculosis [Ehlers S., 2005; Allie N. et al., 2008;

Francisco N.M. et al., 2015]. It is important that the ambiguous effect of this cytokine enhances both Th1- and Th17-dependent reactions of cellular immunity and autoimmunity, as well as the functions of T-regulators and fibroplasia [de Silva A.D, et al., 2018].

Previously, in an experiment on mice, it was shown that the effects of TNF-α in tuberculosis depend on the permissive action of IL-4 [de Silva A.D. et al., 2018], which obviously explains the combined increase in their production recorded by us in patients with PT.

The mean blood level of IFN-γ in patients with PT was significantly higher than in PS patients (185.4±21.2 pg/ml and 146.7±11.3 pg/ml, respectively; $p<0.05$) and in both groups of patients, this indicator is 3.5 and 2.8 times higher than in healthy individuals (50.9±1.6 pg/ml; $p<0.001$). This Th1-dependent cytokine is the main protective factor against persistent intracellular infection, resistance to various infectious granulomatosis and viral infection is associated with it. It suffices to point out the role of determining the increase in the production of this particular cytokine under the action of marker proteins of Mycobacterium tuberculosis in the IGRA diagnostic test (see above). An increase in its concentration in the examined patients obviously reflected the protective processes in PT. But IFN-γ also serves as an important bioregulator in the pathogenesis of sarcoidosis: it has recently been shown that it is under the action of this cytokine, produced by Th17-lymphocytes in PS, that monokines are expressed that contribute to the formation of sarcoid granulomas, in particular MIG (monokine induced by interferon-gamma) [Ragusa F., 2015; Arger N.K. et al., 2020].

Since IL-4 inhibits, and TNF-α, on the contrary, promotes the formation of IFN-γ, it can be assumed that the higher level of IFN-γ in PT, in comparison with PS, was the result of a stronger influence of TNF-α (which, according to to our data, patients with PT produced more than patients with PS) and less action of IL-4 (which they had less than with PS).

In general, it should be noted that there were also certain differences associated with a more intense effect of cytokines that provide cytotoxic immune mechanisms in PT and increased production of cytokines that affect the formation of T-regulators in different directions in PS.

It should be emphasized that the levels of IL-2 (inducer of T-regulators) and IL-6 (inhibitor of T-regulator differentiation) were 1.2 and 3.1 times higher, respectively, in the group of patients with PS than in PT, which could reflect both a violation of the production of T-regulators, and the process of its compensation by the body. These changes may be associated with the course of autoimmune processes in PS. The level of IFN-γ, on the contrary, was 1.3 times higher in the group of patients with PT (apparently, for the reasons already discussed above).

Characteristically, in PS, the average concentration of IL-4 (which contributes to M2 polarization of macrophages of granulomas typical of PS and not characteristic of PT, see above) was 1.3 times higher than in PT.

Apparently, changes in the content of the studied cytokines in patients with PT and PS to a large extent determined the clinical and laboratory picture of the response of the acute phase and ISDA.

The progression of ISDA, as noted above, underlies toxic-septic shock and pre-shock state, which received in 1987-88. not quite correct, from the point of view of general pathology, but rooted in clinical medicine, the name "systemic inflammatory response" [Cerra F.B., 1987; Laurent P.E., 1988]. Based on the cytokine theory of multiple organ failure syndrome (MODS), R.C. Bone (1996), describing the development of events after an acute illness with symptoms of a systemic inflammatory response, that is, a very pronounced ISDA, introduced the term "compensatory anti-inflammatory response" (CARS) with three clinical variants: the predominance of systemic inflammatory response syndrome (SIRS), which ultimately leads to the formation of organ failure; the predominance of CARS ("immune paralysis", increased risk of infectious invasion); and, finally, the balance of SIRS and CARS is the most favorable variant of the inflammatory

process and its systemic correlates, with a high probability of a successful outcome.

In accordance with these ideas, adjusted for the fact that the patients involved in the study were not in a pre-shock state at the time of studying their indicators and had only moderate severity of ISDA, given the above clinical manifestations and laboratory parameters of the course of PT and PS, it can be assumed that that the examined patients had a “compensatory anti-inflammatory response” with manifestations of an imbalance in the pro-inflammatory link of cytokines.

Assessment of humoral adaptive immunity in patients in the 1st, 2nd and control groups was carried out in terms of the average blood concentration of Ig A, Ig M, Ig G and circulating immune complexes (CIC) (table 11).

The average concentration of Ig A was 2.8±0.2 g/l in the group of patients with PT, 2.8±0.1 g/l in patients with PS and 3.1±0.3 g/l in the control group . That is, the concentration of Ig A in the blood in pulmonary patients with PT and PS was the same, but turned out to be slightly lower ($p > 0.05$) than in healthy people [Nikolaev A.V., Churilov L.P., 2020].

The average concentration of Ig M in the blood in patients with PT and PS was also almost the same (2.0±0.3 and 1.9±0.2 g/l, respectively; $p>0.05$), but in both groups it was significantly higher, compared with the control (1.2±0.3 g/l; $p<0.05$) [Nikolaev A.V., Churilov L.P., 2020].

The average concentration of Ig G in the blood of patients with PT was significantly higher (22.6±0.3 g/l) than in patients with PS (19.6±0.2 g/l; $p<0.05$). At the same time, in both groups of patients, the level of Ig G was significantly ($p<0.05$) higher than this indicator of the control group, in which its average value was only 14.6±0.4 g/l [Nikolaev A.V., Churilov L.P., 2020].

The content of low molecular weight CEC (nm) and medium molecular weight CEC (cm) in the blood of patients in the control group was 72.7 ± 4.5 conventional units, respectively. units and 31.3±3.2 arb. units In patients with PT and PS, the content of immune complexes increased significantly ($p<0.05$): CEC

nmm - 1.5 and 1.3 times, respectively, CEC smm - 1.9 and 1.5 times, respectively. That is, both CEC nmm and CEC smm (to an even greater extent) accumulated in the blood of patients with pulmonary granulomatosis [Nikolaev A.V., Churilov L.P., 2020].

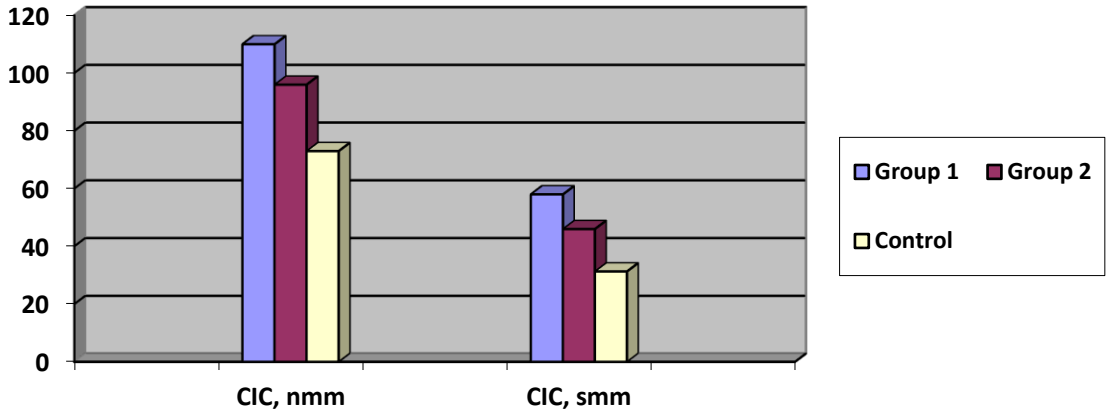
Between the groups of patients with PT and PS, there was a significant difference only in terms of CEC cm ($p<0.05$). In case of dysfunction of the detoxification systems and defects in the mechanisms of IC clearance, it is the CEC smm that are deposited on the endothelium of microvessels, and in the case of counter-diffusion of antibodies and antigen, they are also deposited in tissues, for example, at the alveolar-capillary border and, at the same time, have a greater pro-inflammatory activity than the CEC nmm [Akhmedzhanova Z.M., 2010; Churilov L.P., 2021].

Table 11 - The content of immunoglobulins and CEC in the blood of the examined patients (M ± m)

Показатели	Group 1 (PT; n=53)	Group 2 (PS; n=42)	Control (n=30)
Ig A,г/л	2,8±0,2	2,8±0,1	3,1±0,3
Ig M,г/л	2,0±0,3*	1,9±0,2*	1,2± 0,3
Ig G,г/л	22,6±0,3*	19,6±0,2*#	14,6±0,4
CICn mm, conv. units	109,8±9,8*	96,2±9,5*	72,7±4,5
CICc mm, conv. units	57,8±3,2*	45,8±4,0*#	31,3±3,2

Notes: 1/ * - in the 1st and 2nd groups, the differences in indicators are significant, relative to the corresponding indicators of the control group ($p<0.05$): 2/ # - differences in indicators between the 1st and 2nd groups are significant ($p<0.05$).

In general, the analysis of the results of humoral immunity indicators indicated that in patients with PT and PS, in comparison with the data of healthy donors, there is an inhibition of the synthesis of antibodies of the Ig A class, activation of the synthesis of antibodies of Ig M and Ig G, and an increase in the formation of CIC. These changes were more pronounced in PT, but the difference in mean values in PT and PS was significant ($p<0.05$) only in relation to Ig G and CEC levels cmm - fig. 7.



Pic.7 - The content of CIC nmm and CIC smm (conv. units) in the blood of patients.

Note: the 1st group, the 2nd group and the control group are marked with columns

It was previously shown, including by the method of dynamic light scattering, that in tuberculosis and sarcoidosis different organs of the IC differ, in particular, in the first case, they contain antibodies to mycobacterial antigens, and in the second, to autoantigens of organs affected by sarcoidosis [Starshinova A. et al., 2018], in addition, there are differences in the isotypes of the immunoglobulins contained in these complexes, for individuals who develop PT after a positive tuberculin test, the presence of IgG3 and reagin antibodies is more typical, which is used for prognostic purposes [Starshinova A.A. et al., 2019]. It is possible that, in PT and PS, due to a decrease in the functions of SED, ISDA increases as an equivalent of endotoxicosis, destruction of lung cells occurs. At the same time, according to the theory of immunological clearance, P.N. Grabar - I.E. Kovaleva

(see above), the production of autoantibodies increases, blocking many autoantigens exposed in excess with the formation of the CIC nmm and, to an even greater extent, the CIC smm, which, if accumulated due to impaired utilization, can participate in the formation of a vicious circle of lung damage with progression of the inflammatory reaction and its complications [Sidorova I.S., 2003; Poletaev A.B. et al., 2012].

Prevention of the formation of this kind of vicious circle in diseases with ISDA is based on the inclusion of immunomodulators and detoxification therapy in the courses of complex treatment of patients [V.A. et al., 2013]. The literature indicates that there is a direct dependence of the level of AAT increase on the severity of the destructive process in the target organ, including in the lungs, regardless of the nature of the cause of the alteration of the target organ [Skurydin S.V. et al., 2010 Poletaev A.B., 2019]. This prompted us to compare the spectrum and intensity of autoimmunity in PS and PT.

3.3.1 Intensity and spectrum of autoimmune processes in PS and PT

Since a number of features of the parameters of the immune system in patients with PS and PT could contribute to the activation of its autoreactivity (see above), and earlier manifestations of autoimmunity were noted by a number of authors both in PS and PT, we assessed the spectrum and intensity of autoimmune processes in these forms. pathology. The serum content of a number of pulmotropic autoantibodies (to such lung tissue antigens as: LuM 01-230, LuS 06-300, LuS 06-80) and autoantibodies to other organ-specific and non-organ-specific autoantigens, most often involved in autoimmune processes, was determined.

The indicators presented in Table 12 represent the average values of deviations in the content of autoantibodies (AAT) as a percentage of the norm determined for the pool of reference sera from healthy donors as described above,

in the "Material and Methods" section. The direction of the deviations is reflected by the signs + (in case of increase) or - (in case of decrease).

The levels of AAT to a number of autoantigens in PS and PT changed in different directions in relation to the average individual immunoreactivity, either increasing or decreasing.

Thus, the average value of the increase (in relation to the individual average immunoreactivity) of the content of antibodies to the non-organ-specific antigen of cell nuclei - double-stranded DNA (ds-DNA) was in the group of patients with PS (+8.9 ± 1.5%) compared with the fall of this indicator in the group of patients with PT (-24.1±3.2%), with statistically significant differences between groups of patients ($p<0.05$).

Similarly, the levels of antibodies to the cytoplasmic antigen of neutrophilic granulocytes ANCA in PS increased relative to the average individual immunoreactivity, and in PT, on the contrary, became lower than it (+8.2±1.1% and -10.3±0.9%, respectively) . The difference between the indices in the PS and PT groups was also statistically significant in this case ($p<0.05$).

The level of AT to insulin in patients with PS increased relative to the individual mean by +5.6±1.6%, which was significantly ($p<0.001$) higher than its negative increase in the group of patients with PT (-35.7±8 .2%).

Similarly, the values of the levels of antibodies to the cytoplasmic antigens of the lungs LuS-06 in PS exceeded the individual average immunoreactivity (+4.3±2.5%), but in PT they fell in relation to it (-15.0±2.3%), and the difference between the groups of patients with different granulomatosis was statistically significant ($p<0.05$).

The dynamics of the average values of the concentration of antibodies to the lung membrane antigen LuM-02, in relation to the average levels of immunoreactivity of patients, was also multidirectional, although the lungs were affected by both granulomatosis. The levels of this indicator in PS were slightly higher than the individual average immunoreactivity of patients (+3.5±1.8%), and

in PT they significantly decreased (-33.1±5.4%), and the difference between the groups was, again, , statistically significant ($p<0.05$).

In comparison with the average individual immunoreactivity, there was an increase in the level of antibodies to the myocardial antigen CoM-02 in the group of patients with PS (+3.4±1.1%) and its decrease in patients with PL (-11.2±2.8%; $p<0.05$).

Similarly, the level of antibodies to β2-glycoprotein I increased relative to the individual mean in the PS group (+3.2±0.8%), and fell in the PT group (-32.3±5.8%; $p<0 .05$).

The levels of antibodies to thyroglobulin increased relative to the individual mean in the group of patients with PT (+59.1±4.7%), but fell in PS (-3.6±1.5%) with statistically highly significant differences ($p<0.001$).

The level of antibodies to membrane antigens of cells of the gastric mucosa GaM-02 also increased in patients with PT (+7.9±1.2%) and, with a decrease in the same indicator in the group of patients with PS (-13.6±4.1%), the difference between the groups was statistically significant ($p<0.05$).

In PS and PT in relation to individual autoantigens, the level of AT unidirectionally increased.

Thus, the level of antibodies to MBP in patients with PS and PT in relation to the average individual immunoreactivity was +40.8±15.8%, and +27.8±5.8%, respectively, and the differences between the groups of patients were not statistically significant. ($p>0.05$).

Table 12 - The mean values of the serum levels of autoantibodies in the ELI-test (M±m%).

№№ test/Indicators	Group 1 (PT; n=53)	Group 2 (PS; n=42)
1/ AB for ts-DNA	-24,1±5,7	+ 8,9±5,8*
2/ AB for ANCA	-10,3±4,2	+8,2±5,5*
3/ AB for insuline	35,7±6,6	+5,6±4,7*
4/ AB for LuS-06	-15,0±4,5	+4,3±4,1*
5/ AB for LuM-02	-33,1±6,5	+3,5±3,4*
6/ AB for CoM-02	-11,2±4,2	+3,4±3,3*
7/ AB for β2-glicoprotein I	-32,3±6,4	+3,2±3,1*

8/ AB for thyreoglobulin	+59,1±6,8	-3,6±3,5*
9/ AB for GaM-02	+7,9±3,7	-13,6±7,0*
10/AB for OPM	+40,8±6,8	+27,8±9,2
Continuation of table 12		
11/AT κ β1 adrenoreceptors	+52,3±6,9	+11,6±6,4*
12/ AB for HMMP	+37,3±6,6	+11,3±6,4*
13/ AB for KiS-07	+82,5±5,3	+8,4±5,7*
14/ AB for ItM-07	+2,3±1,9	+4,8±4,5
15/ AB for TSH receptors	+89,3±4,4	+4,5±4,2*
16/ AB for S100	+2,4±2,1	+4,0±3,9
17/ AB for HeS-08	+10,0±4,1	+3,4±3,3
18/ AB for GFAP	-18,6±5,4	-12,3±6,6
19/ AB for Spr-06	-22,5±5,8	-12,5±6,7
20/ AB for TrM-03	-51,1±6,7	-12,8±6,9*
21/ AB for Fc-Ig	-25,0±6,0	-12,8±6,9
22/ AB for KiM-05	-54,8±6,8	-21,3±8,3*
23/ AB for AB for	-40,8±6,8	-29,3±9,3
24/ AB for AdrM-D/C-0	-36,7±6,6	-38,4±9,9

Note: 1/Deciphering the designations of autoantibodies is presented in Chapter 2; 2/* - values of indicators in the 1st and 2nd groups differ significantly ($p < 0.05$-0.001).

The values of AB to β1-adrenergic receptors in both granulomatosis were also higher than the average individual immunoreactivity and amounted to +52.3±6.7% in the PT group and +11.6±3.4% in the PS group, that is, in patients with tuberculosis the level of this indicator increased more significantly than in SL ($p<0.05$).

The increase in the level of autoimmune reactivity in relation to the mitochondrial antigens of the liver HMMP was significantly ($p<0.05$) higher in patients with PT (+37.3±6.7%), compared with the corresponding increase in the PS group (+11.3±2 ,8%).

Both granulomatosis led to an increase in autoimmune reactivity in relation to a number of antigens above the average individual, but to a different extent: the average value of the increase in the AB index to membrane antigens of the small intestine ItM-07 (in relation to the average individual immunoreactivity) in PS

was +4.8± 1.0%, which was significantly ($p<0.05$) higher than the increase in the level of these antibodies in the group of patients with PT (+2.3±0.8%).

On the contrary, the levels of antibodies to TSH receptors increased in relation to the average individual immunoreactivity much more noticeably ($p<0.001$) in the group of patients with PT (+89.3±11.9%) than in the group of patients with PS (+4.5±1 ,4%).

The levels of antibodies to the S100 protein increased in relation to the individual average immunoreactivity in the group of patients with PS slightly more noticeably than in patients with PT (+4.0±0.9% and +2.4±0.6%, respectively), but without statistically significant differences between groups ($p>0.05$).

In both granulomatosis, there was a statistically significant trend towards an increase in the level of autoimmunity to cytoplasmic antigens of the liver HeS-08: +10.0±2.4% in the PT group, higher than in PS (+3.4±1.3%; $p< 0.05$).

Autoimmunity against some autoantigens in both granulomatosis tended to decrease, below the average individual autoimmunoreactivity.

Thus, the levels of AAT to the GFAP protein (specific glial fibrillar acidic protein of astrocyte filaments) in the 1st and 2nd groups of patients were - 18.6±5.4% and - 12.3±6.6% ($p>0 .05$), respectively.

Similar dynamics was also revealed when comparing the level of antibodies to spermatozoa antigens Spr-06 (with PT -22.5±2.9%, with PS -12.5±3.8%).

The concentration of antibodies to platelet antigen TrM-03 in both granulomatosis tended to decrease in relation to the average individual immunoreactivity, but this decrease was statistically significantly more pronounced in PT (-51.1±11.2%) than in PS (-12 .8±4.8%) at $p<0.05$.

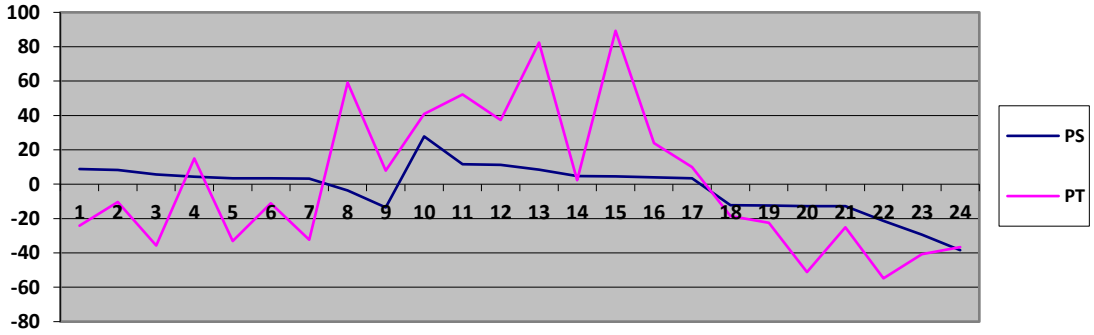
The degree of decrease in the number of rheumatoid factors (AB to Fc-Ig) in relation to the average individual immunoreactivity was -25.0±4.6% and - 12.8±3.1% in PS and PT, respectively, that is, in PS, the number of these antibodies decreased more noticeably than in PL ($p<0.05$).

Differences were statistically significant between unidirectional downward shifts in AB values to kidney membrane autoantigens KiM-05 in the groups of patients with PS and PT (-21.3±7.4% and -54.8±11.3%, respectively; $p<0.05$), and the drop in their level was deeper during PT than during PS.

The levels of antibodies to insulin receptors fell in relation to the average immunoreactivity both in patients with PS (-29.3±6.7%) and in patients with PT (-40.8±5.9%), but the difference between the groups in in this case was not statistically significant ($p>0.05$).

The average values of the level of antibodies to the adrenal glands - AdrM-D/C-0 decreased below the individual averages to approximately the same extent in both groups of patients: - 36.7 ± 4.3% in the group of patients with PT and - 38.4 ± 6.2% in the group of patients with PS ($p>0.05$).

Summing up the analysis of the ELI-test parameters in patients with PT and PS, it should be noted that their autoimmune reactivity profiles differed significantly, with the polar dynamics of a number of indicators, although there were also unidirectional shifts - Pic.8.



Pic.8 - Quantitative ELI-test data in patients with PT and PS.

Note: the numbers on the graph coincide with the order of the data in Table 13, along the y-axis - deviations from the individual average autoimmune reactivity. Indicated by color: PS - blue, PT - red

At the same time, the average values of the levels of Abs to ds-DNA, Abs to β2-glycoprotein I, Abs to Fc-Ig, Abs to CoM-02, Abs to TrM-03, Abs to ANCA, Abs to KiM-05, Abs to LuM -02, Abs to LuS-06, Abs to ItM-07, Abs to insulin,

Abs to insulin receptors, Abs to Spr-06, Abs to S100 and Abs to GFAP increased (+) more pronouncedly (p>0.05 - <0.001) in the group of patients with PS than in patients with PT [Nikolaev A.N. et al., 2020].

The average values of concentrations of antibodies to β1-adrenergic receptors, antibodies to KiS-07, antibodies to GaM-02, antibodies to HeS-08, antibodies to HMMP, antibodies to thyroglobulin, antibodies to TSH receptors and antibodies to MBP increased (+), vice versa , more noticeable in the group of patients with PT than in patients with PS (p> 0.05-<0.001) [Nikolaev A.N. et al., 2020].

Moreover, in the group of patients with PT, the values of the studied parameters with the "+" sign were for 10 different Abs (values of + 30% or more, which are considered abnormal according to the recommendations of the manufacturer of the kits, were present in 6 out of 10 such cases, in particular, for Abs levels to β1-adrenergic receptors, to KiM-05, etc.), and values with a "-" sign were found for 14 types of antibodies (values of -20% or less, which the kit manufacturer recommends referring to as abnormal, were detected in 9 out of 14 such cases , including the levels of AAT to ds-DNA, to β2-glycoprotein I, etc.) [Nikolaev A.N. et al., 2020].

In PS with the "+" sign, there were shifts in the levels of 15 out of 24 studied types of Abs, and a shift of + 27.8% close to an anomaly was only for the dynamics of Abs to MBP, and the rest of the shifts were much less pronounced. With the "-" sign, there were shifts in the levels of 9 types of antibodies (with abnormal values of -20% or less - in 3 cases: for antibodies to KiM-05, to AdrM-D / C-0 and to insulin receptors) [Nikolaev A. N. et al., 2020].

These data indicate a mosaic pattern of damage in the body in PT and PS and that, having a common basis, these granulomatosis differ in pathogenesis and the involvement of different tissues and organs in the immunopathological process.

It should be noted that autoimmune reactivity often changed polarly in PS and PT, which creates the prospect of differential diagnostic use of ELI test data in the diagnosis of PS and PT.

It is noteworthy that in relation to a number of non-organ-specific antigens widely distributed in the body, including the components of cellular apoptotic debris, autoimmunity increased in PS, and decreased in PT in relation to the average individual severity of autoimmune processes. This indicates the actual multiorganism of the process in the diagnosis of PS, regardless of the localization of the main manifestations of granulomatosis, and, obviously, confirms the hypothesis of an autoimmune, autoinflammatory nature of sarcoidosis.

The noncaseating nature of granulomas in PS obviously suggests apoptotic and apoptosis-like pathways of their cell death, respectively, and the level of antibodies to apoptosis products tends to increase.

Their average levels in PT turned out to be very indicative, they fell significantly, even against the background of a generally reduced average individual immunoreactivity in this disease, and in PS, on the contrary, they even became slightly higher than these average levels. Under conditions of destruction of lung tissue by necrotic processes in tuberculous granulomas, the body, apparently, restrains antipulmonary autoimmunity so as not to aggravate alteration of the target organ. But in sarcoidosis, when the granulomas are not necrotic, and cell death is mainly of a regulated apoptotic nature, a high level of autoimmune response to the antigens contained in the products of tissue apoptosis is maintained for the purpose of immune clearance of the apoptotic debris material. Thus, in PS, the response of the immune system (to an unknown causative factor) is relatively active and preserved, in comparison with PT, which indirectly affects the dynamics of antipulmonary autoimmunity.

This confirms the literature data that “the paradox of the body’s immune response to MBT is the simultaneous activation and anergy of immunocompetent cells” [Tang Y., Stratton C. W., 2018]. It is no coincidence that the dynamics of

the level of many antibodies was negative, and for PT - with more pronounced drops than for PS.

Recently, it has been shown that it is a decrease (and not an increase!) in the level of some AATs to nuclear and receptor autoantigens that can be pathogenic, since such autoantibodies are normally functional and perform a regulatory role in healthy individuals [Cabral-Marques, O. et al., 2018; Halpert G. et al., 2020].

In light of this, a decrease in autoimmunity to a number of antigens in PT and PS cannot be interpreted as a sign of sanogenicity or an improvement in the course of the disease. On the contrary, it may reflect the impaired autoimmune regulation of homeostasis in these forms of pathology, that is, the lack of functional AAT involved in the clearance of antigens and/or signal regulation.

3.4 Results of the study of the levels of hormones, vitamin D and cathelicidin in patients with tuberculosis and sarcoidosis of the lungs

In section 3.1. of this chapter, it was mentioned that endocrine pathology (diabetes mellitus, MS, thyroid diseases) was somewhat more common (1.23 times) in patients of the 1st group (in 17 out of 53 people - 32.1 ± 6.4%; in 1 of the patient was combined with each other) than in the 2nd group - in 11 out of 42 (26.2±6.8%; $p>0.05$, three had endocrinopathies in combinations).

We studied the average concentrations of procalcitonin, prolactin, cortisol, thyroid hormones and TSH in the peripheral blood plasma of the subjects - Table 13. The average concentration of procalcitonin in patients with PT (2.3 ± 0.3 ng/ml) was significantly higher than in PS (1 ,1±0.1 ng/ml; $p<0.05$), and in both groups of patients this indicator was statistically significantly ($p<0.05$) higher than in healthy individuals in the control group, in whom procalcitonin detected by immunocompetitive methods was absent in the blood plasma.

Hyperprocalcitoninemia has a parallelism with the degree of ISDA and the severity of concomitant toxic-septic disorders. The procalcitonin generated in this

case does not undergo proteolysis into the definitive hormone and serves as a marker of inflammation, in particular, of the organs of the respiratory system, and a correlate of the degree of ISDA, and, in general, it characterizes the presence of bacterial inflammation and a violation of the barrier function of the latter, since its concentration does not increase somewhat significantly in most viral and aseptic, for example, autoimmune inflammations, if there is no bacterial co-infection or provocation of the process by bacteria [Nikolaev A.N. et al., 2020; Limper M. et al., 2010; Schuetz P. et al., 2011; Abedini A. et al., 2019].

The presence of hyperprocalcitoninemia in tuberculosis was previously noted in a number of studies; some authors even attach prognostic value to this parameter in PT and tuberculous meningitis as a correlate of severe course and lethal outcome of tuberculosis [Nikolaev A.N. et al., 2020; Kim J. et al., 2016; Osawa T. et al., 2020]. In non-tuberculous community-acquired pneumonia of bacterial etiology and infectious complications of chronic obstructive pulmonary disease, even higher levels of procalcitonin were found [Ugajin M. et al., 2011]. Therefore, this symptom cannot be considered specific for tuberculosis infection; moreover, it is not suitable for differentiation from non-tuberculous bronchopulmonary infections, in which procalcitonin levels are usually higher. This marker is not considered by all authors to be adequate specifically for PT (although attempts have been made to link it with PT), because the level of this acute phase reactant depends more on the severity of the bacterial inflammatory process and the violation of its locality than on its specific etiology [Nikolaev A.N. et al., 2020; Naderi M. et al., 2009; Aggarwal D. et al., 2011; Ben Amar J. et al., 2016]. Even with COVID-19, hyperprocalcitoninemia was noted and served as an unfavorable prognostic factor, although this is a viral disease, as it was associated with the degree of ISDA and bacterial complications of acute respiratory distress syndrome [Del Sole F. et al., 2020]. The results of our study presented above are consistent with the known data on the exchange of procalcitonin in PT As for PS, although the question of the level of procalcitonin in this disease is important both for biomedicine, in terms of the still unknown

etiology of this disease, and for applied health care, in terms of differential diagnosis of infectious and non-infectious bronchopulmonary diseases, and, moreover, the question this one has been directly stated in the literature for a long time [Limper M. et al, 2010], but so far no one has given a specific answer to it, since earlier in the world literature there were no studies on the level of procalcitonin in PS [Nikolaev A.N. et al., 2020].

Our study demonstrates for the first time that hyperprocalcitoninemia also occurs in PS, which, first of all, supports the point of view of the authors who do not consider this test significant in the differential diagnosis of PT.

The interpretation of these data can be even broader and, moreover, twofold: either we must admit that hyperprocalcitoninemia is another evidence in favor of the infectious etiology of PS (see above), or we must consider the point of view of those authors who give the test for procalcitonin exceptional significance in the differentiation of infectious and aseptic cases of inflammation and their accompanying acute phase responses [Nikolaev A.N. et al., 2020; Tsogoeva L.M. et al., 2014]. Since hypercalcemia often occurs in sarcoidosis, and even calcitonin is used as a treatment for such cases [Nikolaev A.N. et al., 2020; Rúa-Figueroa I. et al., 2002], it is possible that procalcitonin in PS is partially of neuroendocrine origin, and thus hyperprocalcitoninemia in it is a manifestation of a compensatory reaction of the body against calcium metabolism disorders.

The mean cortisol level in patients with PT was 942.3±36.5 nmol/l and was higher than in patients with PS — 895.4±42.6 nmol/l (although there were no differences between groups 1 and 2). statistically significant - $p>0.05$). At the same time, the average concentrations of cortisol in the blood of patients in both groups were significantly higher (by 1.7 and 1.6 times, respectively) than in practically healthy people - 543.2±45.5 nmol/l ($p<0.001$) [Nikolaev A.N. et al., 2020].

We interpret the trend towards hypercortisolism in PS and PT as the result of a protective moderating effect of stress mechanisms on the potentially shock-producing acute phase response in ISDA (“endotoxicosis”). In PT, the

manifestations of the latter, in particular, the symptoms of ISDA, were more pronounced (see above); accordingly, the level of stress balancing these pro-inflammatory effects was also higher. The hyperproduction of cortisol as a factor of sanogenetic neuroendocrine influence in the pathogenesis of tuberculosis was indicated earlier [Nikolaev A.N. et al., 2020; Bottasso O. et al., 2007].

The average concentration of T3 in the groups of patients with PT and PS was practically the same (1.3±0.1 nmol/l and 1.2±0.1 nmol/l, respectively; $p>0.05$), but in both groups of patients it turned out to be significantly lower than in the control group (1.7±0.1 nmol/l; ($p<0.05$) [Nikolaev A.N. et al., 2021].

This fact is regarded by us as a manifestation of characteristic for cachectic and shock-like conditions (both infectious and non-infectious etiology) and chronic ISDA - the syndrome of "low triiodothyronine". Under conditions of hypercytokinemia and, more broadly, ISDA, as well as a shortage of resources redirected by the response of the acute phase and stress from the somatic sector of the body to the organs and tissues listed above, thyroxine deiodination is inhibited and the effects of the most active of the thyroid hormones, triiodothyronine, are reduced, so as not to aggravate metabolic deprivation through stimulation of basal metabolism. A similar phenomenon was noted both experimentally with the action of pro-inflammatory autacoids on rats, and in the clinic, for example, in malnourished patients and in persons on dialysis due to endogenous intoxications, and recently in severe complicated course of a new coronavirus infection [Nikolaev A.N. et al., 2021; Gao W. et al., 2020].

It has been proven that higher levels of pro-inflammatory cytokines, a greater intensity of the acute phase response and ISDA correlate with lower concentrations of T3. Under these conditions, the body, as it were, is “not in a hurry” to live, reducing the concentration of the most powerful stimulant of the main metabolism - T3 [Nikolaev A.N. et al., 2021; Boelen A. et al., 2006; Lubrano V. et al., 2010; Yavuz D. et al., 2014; Mancini A. et al., 2016; Črne Fureš N. et al., 2018]. Similar changes were observed in the intergroup comparison of the average concentration in the blood of T4: in the control group, the value of the indicator

was 97.0±1.7 nmol/l, and in the groups of patients with PT and PS this indicator was significantly ($p<0.05$) lower - 78 .2±4.6 nmol/l and 67.2±8.2 nmol/l, respectively. Differences in the average level of T4 in the blood in the group of patients with PT were not statistically significant ($p>0.05$), compared with those in PS.

In this regard, we note that similar changes, in particular, a low level of triiodothyronine in general euthyroidism, are also characteristic of some autoimmune chronic diseases, in particular, chronic fatigue syndrome [Nikolaev A.N. et al., 2021; Ruiz-Núñez B. et al., 2018].

Mean TSH levels in the groups of patients with PT and PS were 4.7±0.7 and 3.6±0.5 nmol/l, respectively ($p>0.05$) and were significantly ($p<0.05$) higher than in the control group - 2.2±0.6 nmol/l. Consequently, euthyroidism in these groups of patients was maintained at the cost of greater tension in the compensatory hypothalamic-pituitary mechanisms. This is characteristic of the initial subclinical stages of thyroid disorders occurring, in particular, in autoimmune Hashimoto's thyroiditis and later progresses to subclinical hypothyroidism, typical of this disease, often combined with granulomatosis. The TSH levels registered in the groups of patients with PT and PS, in the light of new recommendations based on population cohort studies on narrowing the normal range of thyrotropin concentrations to 0.3-2.5 mU/ml, correspond to the level of moderate subclinical hypothyroidism [Nikolaev A.N. et al., 2021; Brabant G., 2009].

Table 13 - Levels of hormones in the blood of the examined persons (M ± m)

Indicators	Group 1 (PT; n=53)	Group 2 (PS; n=42)	Control (n=38)
procalcitonin, ng/ml	2,3±0,2*	1,1±0,1*#	0,0±0,0
Cortisol, nmol/l	942,3±36,5*	895,4±42,6*	543,2±45,5
T3, nmol/l	1,3±0,1*	1,2±0,1*	1,7±0,1
T4, nmol/l	78,2±4,6*	67,2±8,2*	97,0±1,7

TSH, mlU/k	4,7±0,7*	3,6±0,5*	2,2±0,6
Prolactin, ng/ml	11,2±2,5*	9,5±1,1*	6,9±1,3
25(OH)D, ng/ml	9,8 ± 1,3*	13,2 ± 1,5*	19,3 ± 1,6
Continuation of table 13			
Indicators	Group 1 (PT; n=53)	Group 2 (PS; n=42)	Control (n=38)
1.25(OH)2D, pg/ml	36,4 ± 1,4	50.4 ± 1,6*#	35,5 ±1,9
Cathelicidin, ng/ml	47,1 ± 2,2*	39,8 ± 1,6#	39,8 ± 2,1

Notes: 1/ *- differences in indicators in the 1st and 2nd groups are significant in comparison with the data of the control group ($p<0.05$-0.001); 2/ # - differences in indicators between the 1st and 2nd groups are significant ($p<0.05$)

The mean prolactin concentration in patients with PT was slightly higher than in patients with PS (11.2±2.5 ng/ml and 9.5±1.7 ng/ml, respectively, at $p>0.05$ for intergroup differences) . At the same time, in both groups of pulmonary patients, the average value of this parameter was significantly higher than in the control group (6.9±1.3 ng/ml; $p<0.05$).

The increase in the level of prolactin in the groups of patients was explained, from our point of view, by their tendency to subclinical hypothyroidism (see above). The increased level of TSH production in these groups was apparently achieved by increased hypothalamic stimulation of TSH production. And thyroliberin, which is responsible for increased secretion of TSH during compensation of hypothyroid conditions, is at the same time a pronounced prolactoliberin, therefore, the tendency to hyperprolactinemia against the background of compensation for hypothyroidism, including its subclinical severity, is very typical [Nikolaev A.N. . et al., 2021; Stroev Yu.I., Churilov L.P., 2017; Triggianese P. et al., 2015; Ansari M.S., Almalki M.H., 2016]. A characteristic combination of an increase in TSH levels with a decrease in T3 and T4 levels - with a high level of prolactin was noted by N.K. Borisova et al. (1994),

although they did not link this to the mechanism described above, which was little known at the time.

The revealed tendency to hyperprolactinemia in pulmonary chronic granulomatosis is most likely pathogenetically important.

On the one hand, prolactin is an immunostimulant, and its action involves natural killers, participants in chronic granulomatous inflammation, whose role is essential in anti-infective and antitumor protection.

But, on the other hand, prolactin is a paracrine and endocrine activator of autoimmune processes and can enhance the manifestations of autoimmunity in chronic granulomatous inflammation [Nikolaev A.N. et al., 2021; Triggianese P. et al., 2015; Borba V.V. et al., 2018].

An increase in the level of prolactin was previously noted in PT and was considered an element of neuroimmunoendocrine interactions in this disease [Nikolaev A.N. et al., 2021; Bottasso O. ut al., 2007; 2009]. Moreover, mycobacterial proteins in the experiment strongly stimulate paracrine production of prolactin in macrophage cells [López-Rincón G. et al., 2015], which may contribute to the mechanism of development of this manifestation in patients in vivo as well. Prolactin significantly modulates the cytokine response in RT, enhancing the inflammatory activation of macrophages and promoting apoptotic processes in granulomas, and this hormone has a restraining effect on the production of a number of pro-inflammatory cytokines (TNFα, IL-1β, IL-12), but promotes the production of fibrogenic IL-10 [Nikolaev A.N. et al., 2021; López-Rincón G. et al., 2015; Martinez-Neri P.A. et al. 2015].

In sarcoidosis, hyperprolactinemia is also often noted, and far from always (although often) it accompanies neurosarcoidosis with direct involvement of the diencephalon and pituitary gland [Pushkarev M.S. et al., 2019]. It has been shown that SL without CNS involvement can also occur with hyperprolactinemia [Nikolaev A.N. et al., 2021; Munt P.W. et al., 1975; Nakao K. at al., 1978; Studdy P.R. et al., 1980; Borisova N.K. et al., 1994]. Obviously, the above mechanism associated with the compensation of hypothyroidism is also relevant here.

Prolactin stimulates the activation of calcifediol by converting it into calcitriol [Subramanian P. et al., 2004], therefore, against the background of the tendency towards prolactin hyperproduction inherent in pulmonary granulomatosis, the status of the metabolism of vitamin D and its derivatives was of interest.

According to the literature, in autoimmune and chronic inflammatory diseases, including PT and PS, there is often a deficiency of vitamin D that contributes to autoimmunity (as well as the persistence of chronic infection), which confirms a decrease in its concentration in the blood of patients to a level of less than 20 ng / l [Nnoaham K.E., Clarke A., 2008; Shapira Y. et al., 2010].

In our studies in groups of patients with pulmonary granulomatosis, the average level of the monohydroxylated form of vitamin D (calcifediol, 25 (OH) D) in blood plasma was very significantly below the limit recommended by the literature as the threshold of deficiency - as in PT (9.8 ± 1.3 ng/ml; $p < 0.001$) and in PS (13.2 ± 1.5 ng/ml; $p < 0.05$), and it was lower than in healthy donors. But even in healthy people living in the northern metropolis, which is St. Petersburg, the content of this vitamin in the blood turned out to be at the above-mentioned deficiency threshold (19.3 ± 1.6 ng / ml). It is possible that this general trend with low levels in the blood of the examined persons is also due to the fact that blood samples for analysis were taken from patients from April to June, when insolation in the area of St. Petersburg is still relatively low. However, numerous data obtained in sufficiently sunny regions of the Earth and, moreover, in the summer season, revealed a similar trend when it came to city dwellers. Thus, similar low levels of vitamin D in the blood are recorded in healthy citizens in Israel [Watad A. et al., 2017]. Obviously, the domestication of citizens, who both work and rest, mainly indoors, matters.

There is evidence that with a deficiency of the active vitamin D precursor calcifediol 25 (OH) D, the level of the active dihydroxylated form of the vitamin, calcitriol 1,25 (OH) 2D, produced from it, increases in the body [Zadshir A. et al., 2005].

Calcitriol is formed intracellularly, is fat-soluble and is present in the blood in minor amounts compared to its predecessor.

In our study, the mean serum levels of calcitriol in the control group were 35.5 ± 1.9 pg/ml, in PT they were almost the same (36.4 ± 1.4 pg/ml), and in PS they increased significantly (50.4 ± 1.6 pg/ml). Thus, in PS, this indicator was statistically significantly higher than in patients with PT and in healthy individuals ($p < 0.001$).

These data confirm that the status of vitamin D metabolism in two similar granulomatosis is significantly different. Sarcoid granulomas, in contrast to tuberculosis necrotizing granulomas, are known to be a source of additional dihydroxylated vitamin D, since their macrophages have increased activity of the parathormone-insensitive form of 1α-hydroxylase. In view of this, a decrease in the level of calcifediol with an increased level of calcitriol is especially characteristic of sarcoidosis [Gwadera Ł. et al., 2019; Zhou Y., Lower E.E., 2020]. But it is calcitriol that contributes to the M2 polarization of macrophages, which is typical for PS and not typical for PT [Zhu X. et al., 2018], which is consistent with our data on the increase in its production in patients with PS.

The conversion of calcifediol to calcitriol occurs in the cells of the immune system (except for macrophages, it is also possible in lymphocytes), and it is necessary for their antibacterial activity due to the induction of cathelicidin (human peptide LL-37), a powerful natural animal antibiotic and universal chemokine [Gombart A.F. et al., 2005: Blischak J.D. et al., 2015]. Therefore, it could be expected that the tendency to hypovitaminosis D would affect the provision of the innate immunity system with this antibiotic peptide in patients.

The average concentration of cathelicidin in freshly obtained blood plasma was: in the control group - 39.8 ± 2.1 ng/ml, in PT - 47.1 ± 2.2 ng/ml, in PS - 39.8 ± 1.6 ng/ml ml. That is, the concentration of cathelicidin was significantly increased in PT, in comparison with the data characteristic of PS patients and healthy people ($p < 0.05$).

Similar data with an even greater increase in the level of cathelicidin in PT were also recorded by other researchers who studied the levels of vitamin D and cathelicidin in PT, however, not on freshly obtained plasma, as in our study, but on blood serum, where neutrophils could give additional cathelicidin during coagulation [Yamshchikov A.V. et al., 2010].

At the same time, in case of nonspecific pulmonary pathology of an inflammatory nature, the concentration of cathelicidin in the blood of patients, as a rule, is not higher than in healthy people [Lambert A.A. et al., 2014]. The intracrine cathelicidin response according to these, as well as according to our data, was especially significant for infections with intracellular persistence of the pathogen, which is PT.

The infectious nature of PS has not been proven, and the persistence of pathogens in macrophage cells is uncharacteristic for it, which, in our opinion, explains the lower level of cathelicidin characteristic of such patients.

Cathelicidin is an important vitamin D-dependent element of antimycobacterial immune defense [Ayelign B. et al., 2020]. It has been proven that this is the object of a counter-immune response from mycobacteria, seeking to undermine this reaction of infected cells [Padhi A. Et al., 2019].

This counter-immune action of Mycobacterium tuberculosis is opposed by vitamin D [Rode A.K. et al., 2017].

In our sample, although the levels of vitamin D and its active form were lower in PT than in PS, the cathelicidin response was nevertheless quite pronounced in PT. In our opinion, the role of an additional stimulating factor for the production of cathelicidin in PT could be played by prolactin, the level of which in PT increased more significantly in comparison with healthy donors than in PS.

The relationship between prolactin and cathelicidins in humans was practically not studied before our work. But it is known from zoological studies that cathelicidin is expressed in mammary gland cells during lactation in mammals and is an important factor in early anti-infective protection in

marsupials, which also supplement their offspring during their stay in the pouch with a milk-like secret. In both cases, the production of cathelicidin depends on the effect of prolactin, which stimulates it [Armogida S.A. et al., 2004; Peel E. et al., 2016]. In some models, in particular, in hypoxic necrobiosis of kidney cells, it has been shown that it is cathelicidin that promotes a shift in the polarization of macrophages in the M2 direction, preventing the action of free radicals and necrobiotic alteration of cells, promoting repair processes [Chou H.C., Chen C.M.. 2019].

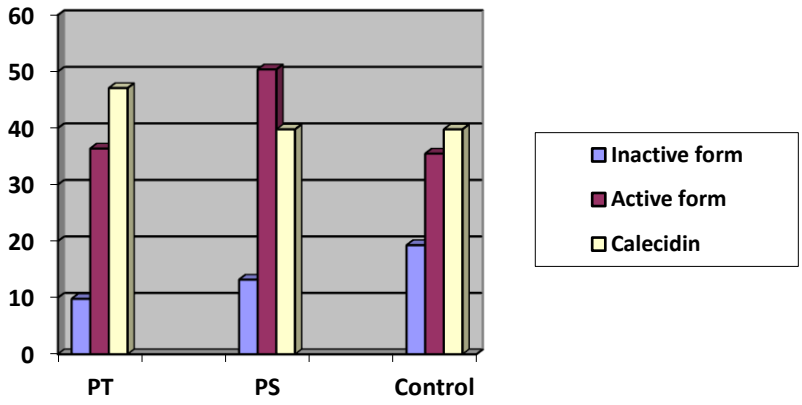
In light of this, it is possible that, in pulmonary granulomatosis, a more pronounced cathelicidin response, characteristic of PT, is compensatory associated with the necrotic nature of tuberculous granulomas and the need to resist necrobiotic processes and the action of an excess of pro-inflammatory mediators, the systemic effect of which in the PT group was more pronounced than in PS.

At the same time, the examined patients, including those in the control group, were found to be deficient in calcifediol. most pronounced in PT. Mobilization of immunity was achieved compensatory by increasing the concentration of the active form of the vitamin - calcitriol, primarily in PS. At the same time, in PT the indicator reached the level of healthy people, and in PS it was significantly higher ($p < 0.001$) than in other groups. At the same time, it was noted that the average concentration of cathelicidin was significantly increased in PT, in comparison with the data in PS and in healthy people ($p < 0.05$) - fig. 9.

It has been proven that calcitriol induces metabolic changes in dendrocytes that contribute to their influence, stimulating the differentiation of T-regulators [Vanherwegen A.S. et al., 2019].

On the model of periodontitis, it was shown that calcitriol prevented the differentiation of T-lymphocytes in the direction of Th17 and Th2 associated with autoimmune reactions [Bi C.S. et al., 2020]. Thus, it is possible to link differences in calcitriol production and autoimmune status in PS and PT.

Comparison of blood hormone levels in patients with PT, PS and in healthy people showed that the levels of procalcitonin, cortisol, TSH and prolactin were higher in pulmonary patients compared to those in the control group. The concentration of thyroid hormones was significantly lower in patients with PT and, especially, PS than in controls. The levels of all studied hormones in the blood in the 1st group of patients with PT were higher than in patients of the 2nd group with PS, but only procalcitonin differences were statistically significant ($p<0.05$).



Pic.9 - Mean blood levels of inactive, active forms of vitamin D and cathelicidin in examined patients.

Both in PT and PS, according to our data, there were features of the metabolic response that promote autoimmunity. In PS, this was the absence of a cathelicidin response, and in PT, relatively higher levels of prolactin, and low levels of calcitriol and calcifediol. Accordingly, having certain manifestations of autoimmunity, in relation to a number of autoantigens, patients with PS and PT differed in intensity and even in the sign of the observed changes in the autoimmune spectrum. The immunoendocrine changes identified in our study complement the complex of differential diagnostic features of these granulomatosis. For example, hyperprocalcitoninemia in PS and combined changes in prolactin and cathelicidin in PT were revealed by us for the first time and have not previously been covered in the available world literature.

CHAPTER 4 STRUCTURE AND FUNCTIONAL STATE OF LUNGS BASED OF INSTRUMENTAL AND RADIATION DIAGNOSTICS IN PATIENTS WITH TUBERCULOSIS AND SARCOIDOSIS

The multidirectional clinical and laboratory data presented above in pulmonary tuberculosis and pulmonary sarcoidosis suggested signs of the same trend detected by instrumental and radiological methods.

4.1 Examination of the function of external respiration in PS and PT

The study of the function of external respiration showed that no one had a compensatory increase in lung capacity (LC) in the 1st group, and in SL it was observed only in three patients (7.1±3.9%; p>0, 05).

Normal LC was noted in 9.4±4.0% of cases with PT and in 66.7±7.2% of cases with SL (7.1 times more often), the intergroup difference of these values was highly statistically significant (p<0.001) - tab. 14.

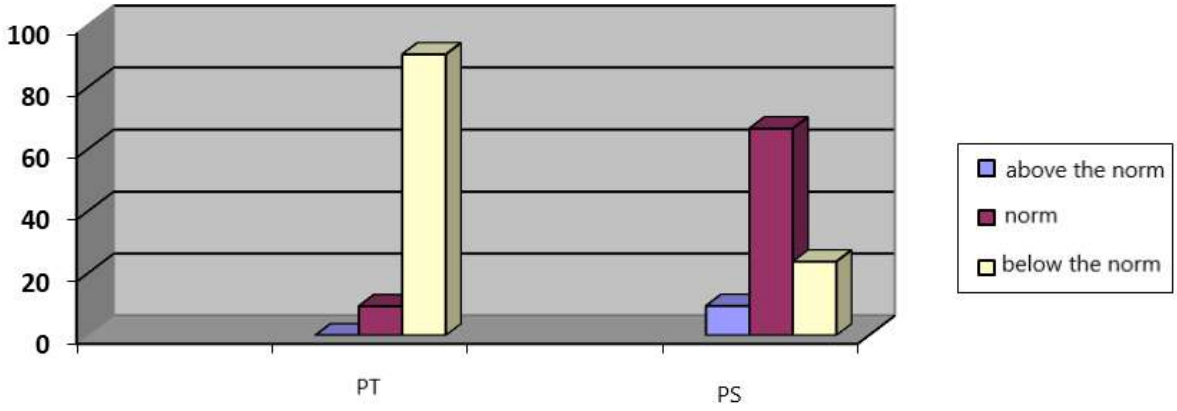
A decrease in LC, on the contrary, was more often recorded in PT - in 90.6±3.9% of patients, that is, 3.8 times more often than in PS (23.8±6.6%; differences are statistically significant at p <0.001).

Table 14 - Frequency of changes in the VC index in patients with PT and PS (M±m%)

Types of infringements	Group 1 (n=53)		Group 2 (n=42)	
	Abs.	M±м %	Abs.	M±м%
Above the norm	-	0,0±0,0	4	9,5±4,6
Norm	5	9,4±4,0	28	66,7±7,2#
Below normal	48	90,6±3,9	10	23,8±6,6 #

Note: #- The difference in indicators in the 1st and 2nd groups is statistically highly significant (p<0.001). Thus, it was found that increased and normal LC (76.2% in total) was recorded in PS 7.9 times more often (p> 0.05-<0.001) than

in PT, which was characterized by a decrease in the indicator LC below normal (90.6±3.9%) - fig. 10.



Pic. 10 - Frequency of changes in LC parameters in PT and PS (%)

Changes in the frequency of the mean rate of forced LC (FVC) in patients with PT and PS were similar to changes in LC (Table 15). A compensatory increase in FVC was found only in two patients with SL 4.8 ± 3.4% and not once in PT ($p > 0.05$).

Normal FVC values were recorded in 66.7±7.2% of patients with PS, i.e., highly significantly ($p<0.001$) more often than in patients with PT, in whom this indicator was within the normal range only in 11.3±4 .3% cases.

A decrease in the mean FVC below the norm was observed in 28.6±7.0% of patients with PS, that is, 3.1 times less often than in patients with PT, in which this parameter was mainly reduced (88.7± 4.3%, $p<0.001$).

Table 15 - The frequency of changes in the FVC index in patients with tuberculosis and sarcoidosis of the lungs (M±m%)

Types of infringements	Group 1 (n=53)		Group 2 (n=42)	
	Abs.	M±м%	Abs.	M±м%
Above the norm	-	0.0±0.0	2	4.8 ±3.4
Norm	6	11.3± 4.3%	28	66.7±7.2#
Below normal	47	88.7±4.3	12	28.6±7.0#

Note: #- The difference in frequency indicators in the 1st and 2nd groups is statistically high - significant ($p<0.001$).

The results of the average forced expiratory volume in 1 second (FEV1) in the examined patients are presented in Table 16.

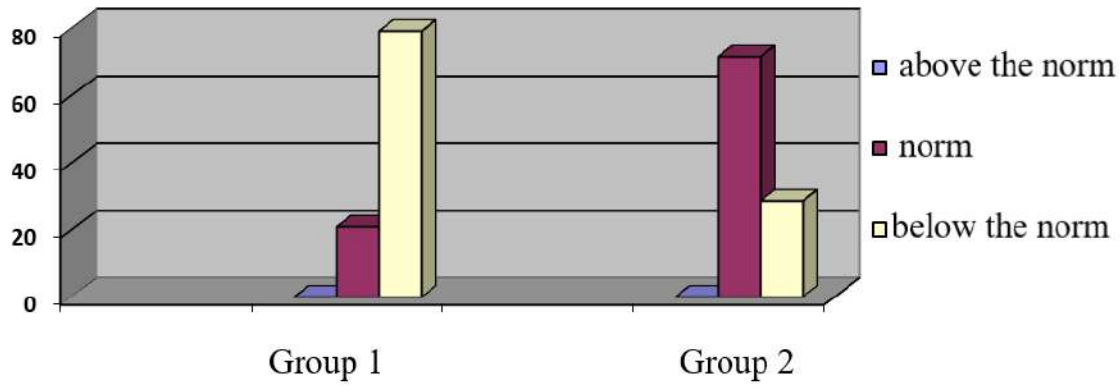
Above the norm, this indicator in pulmonary patients was never recorded. In the group of patients with PS, a normal FEV1 index was maintained 3.4 times significantly more often than with PT (with PS - in 71.4±7.0%, with PT - in 20.8±5.6%; $p<0.001$).

On the contrary, a significant decrease in FEV1 by 2.8 times more often was observed in patients with PT (in 79.2±5.6% of cases) than in patients with PS (in 28.6±7.0%; $p<0.001$).

Table 16 - Frequency of changes in FEV1 in patients with tuberculosis and pulmonary sarcoidosis (M±m%)

Types of infringements	Group 1 n=53)		Group 2 (n=42)	
	Abs.	M±м%	Abs.	M±м%
above the norm	-	-	-	-
Norm	11	20,8±5,6	30	71,4±7,0#
Below normal	42	79,2±5,6	12	28,6±7,0#

Note: # - The difference in frequency indicators in the 1st and 2nd groups is highly significant ($p<0.001$). That is, in patients with PT, compared with PS, signs of restrictive type of ventilation respiratory failure were much more common. - pic.11.



Pic. 11 - Frequency of variants of FEV1 indicators in patients with tuberculosis and sarcoidosis of the lungs (%)

To assess the problems of the capacity of the trachea and bronchi, the dynamics of lung ventilation, changes in the Tiffno-Watchal index (the ratio of FEV1 / VC indicators) were studied. Normally, this ratio is more than 70%; the value of the indicator 50-65% means the initial (reversible) level of bronchial obstruction; 35-50% - average (irreversible) level of obstruction; less than 35% - severe (progressive, leading to disability) level of airway obstruction [Brazhenko N.A., Brazhenko O.N., 2017].

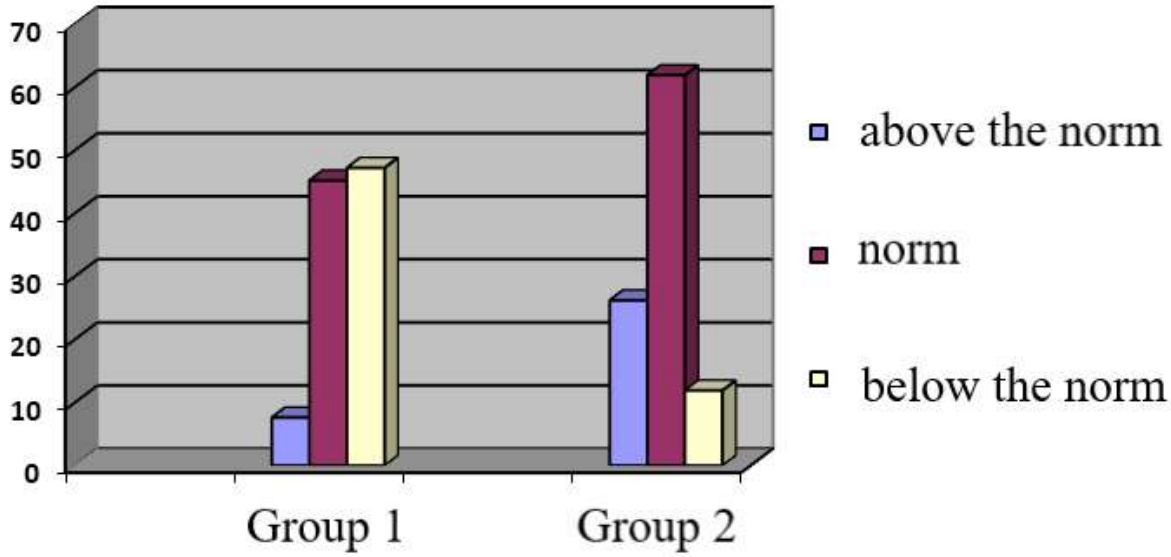
Most patients from the 1st and 2nd groups were in a compensated state, and therefore the values of the Tiffno-Watchal index "below the norm" were detected relatively rarely, in 7.6±3.7% of patients with PT and in 26.2±6 .8% ($p<0.05$) of patients with PS, that is, in the latter group significantly and 3.3 times more often (table 17).

In other cases, the values of this calculated indicator were either "above the norm" (in PT and PS - in 47.2±6.9% and 11.9±5.0%, respectively; $p<0.001$; 4-fold difference), or were “normal” (in 45.2±6.8% of patients with PT and in 61.9±7.5% of patients in the PS group; $p>0.05$).

Table 17 - The frequency of changes in the Tiffno-Watchal index in patients with tuberculosis and sarcoidosis of the lungs (M ± m %)

	Group 1 n=53)		Group 2 (n=42)	
	Abs.	M±м%	Abs.	M±м%
above the norm	25	47,2±6,9	5	11,9±5,0#
Norm	24	45,2±6,8	26	61,9±7,5
Below normal	4	7,6±3,7	11	26,2±6,8#

Note: # - The difference in frequency indicators in the 1st and 2nd groups is significant ($p<0.05$-0.001). Thus, in general, signs of an obstructive pattern of ventilation respiratory failure in PT and PS are rare, but they are much more typical for patients with PS (in every fourth case) - Pic. 12.



Pic.12 - The frequency of changes in the Tiffno index in tuberculosis and sarcoidosis of the lungs (%).

Further, in the groups of examined pulmonary patients, a comparison was made of the maximum volumetric air velocity (MVV25, MVV 50 and MVV 75) of air at the level of exhalation of 25%, 50% and 75% of FVC remaining in the lungs. These indicators reflect the functional conductivity of the bronchi and bronchioles [Zilber A.P., 1989].

Table 18 - Frequency of changes in the MOS25 index in patients with tuberculosis and sarcoidosis of the lungs (M±m%)

Types of infringements	Group 1 n=53)		Group 2 (n=42)	
	Abs.	M±м %	Abs	M±м%
above the norm	3	5,7±3,3	3	7,1±3,9
Norm	43	81,1±5,4	30	71,4±7,0
Below normal	7	13,2±4,6	9	21,4±6,3

Note: The difference in frequency indicators in the 1st and 2nd groups is not significant (p>0.05).

The frequency of MVV25 indicators "above normal", "normal" and "below normal" in patients with PT and PS differed little (p>0.05), more often in the variant "above normal" and "normal" (total in 86.8 % and 78.5% of tests, respectively; p>0.05) - table 18.

MVV 25 was below normal more often in PL than in PT (approximately 1.6 times, respectively, 21.4±6.3% and 13.2±4.6%, at p>0.05).

Normal values of MVV 50, as well as MVV 25, were more often determined in patients with PT (79.2±5.6% of patients) than in patients with PS (66.7±7.3% of patients) - Table. 19.

MVV 50 values above the norm were also more often detected in the group of patients with PT (7.6±3.7%) than in the group of patients with PS (4.8±3.7%; p>0.05). A decrease in the level of MVV 50 below the norm more often (2.2 times) accompanied the course of PS (28.6±7.0% of cases) than PT (13.2±4.6% of cases; p>0.05).

Table 19 - The frequency of changes in the MVV 50 index in patients with tuberculosis and sarcoidosis of the lungs (M ± m%)

Types of infringements	Group 1 n=53)		Group 2 (n=42)	
	Абс.	M±м %	Абс.	M±м %
above the norm	4	7,6± 3,7	2	4,8±3,7
Norm	42	79,2±5,6	28	66,7±7,3
Below normal	7	13,2±4,6	12	28,6±7,0

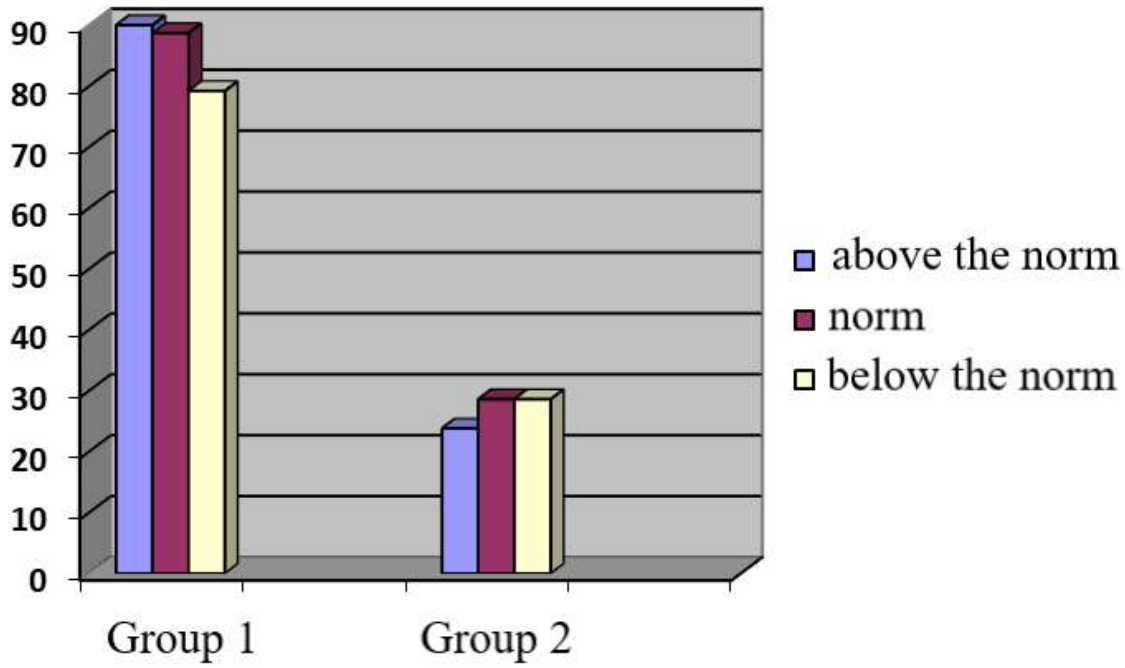
Note: The difference in frequency indicators in the 1st and 2nd groups is not significant (p>0.05).

When comparing the values of the MVV75 indicator, it was found that its normal values were significantly more common (p<0.05) in the group of patients with PT than in the group of patients with PS (in 77.3±5.8 and 54.8±7.7 % of patients, respectively) (Table 20). At the same time, the value of the indicator was above the norm only in the group of tuberculosis patients (in 7.6±3.6%), and in PS - it was not noted even once (p<0.05). On the other hand, in PS, 3 times more often than in PT, the MVV75 index was below the norm (in 45.2±7.7% and in 15.1±4.9%, respectively; p<0.01).

Table 20 - Frequency of changes in the MVV75 index in patients with tuberculosis and sarcoidosis of the lungs (M ± m %)

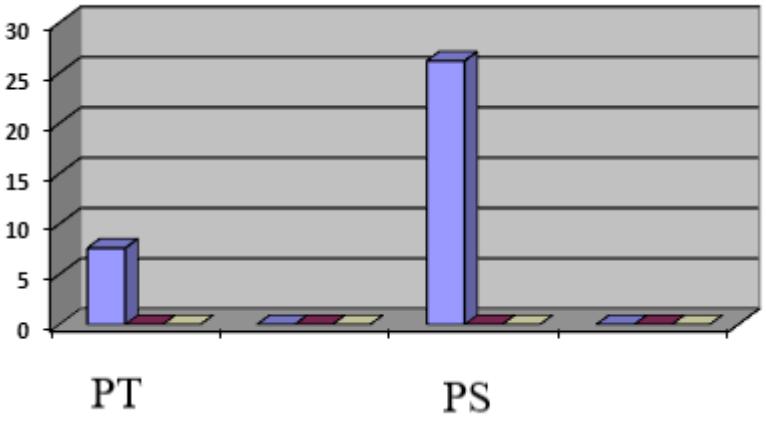
Types of infringements	Group 1 (n=53)		Group 2 (n=42)	
	Abs.	M±м %	Abs.	M±м %
Above the norm	4	7,6±3,6	-	0,0±0,0#
Norm	41	77,9±5,8	23	54,8±7,7#
Below normal	8	15,1±4,9	19	45,2±7,7#

Note: # - The difference in frequency indicators in the 1st and 2nd groups is significant (p<0.05). Of all three indicators MVV25, MVV50 and MVV75, the latter is considered the most informative [Galinskaya L.A., 2013]. In our observations in general, when comparing the frequency values of the MVV25, MVV 50 and MVV 75 indicators, statistically significant differences in frequencies in the PS and PT groups were observed precisely for the MVV75 parameter. Normal values of these tests were more often detected in patients with PT, while values below the norm were more common among patients with PS. Thus, with the help of functional tests, three features were revealed: 1. Volumetric indicators of the function of external respiration were more often reduced in PT, and this was less typical for PS – pic. 13.



Pic.13 - The frequency of indicators of VC, FVC and FEV1 "below normal" in tuberculosis and sarcoidosis of the lungs (%).

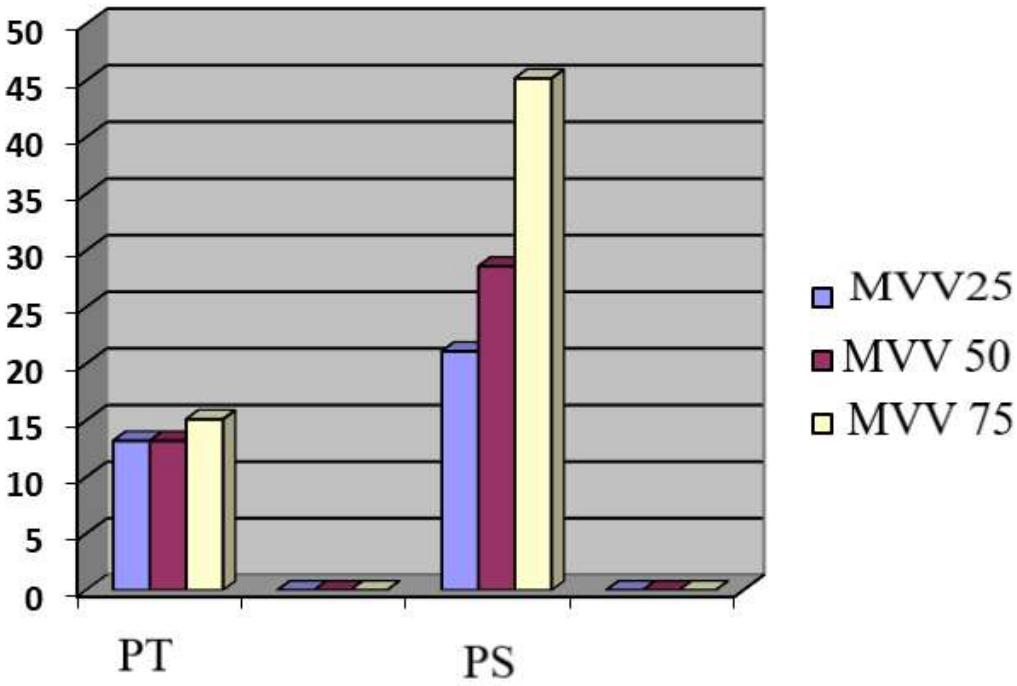
On the contrary, the Tiffno-Watchal index “below the norm” was detected in every fourth patient with PS and more often than with PT, by 3.3 times - pic. 14.



Pic. 14 - The frequency of "below the norm" in the Tiffno index for tuberculosis and sarcoidosis of the lungs (%).

Among the indicators MVV25, MVV50 and MVV 75, reflecting the conductivity of the bronchial system, the latter turned out to be the most informative, and in general the “below normal” variant in PS occurred in 20.9%,

29.2% and 45.8% of cases, which was 1.6, 2.2 and 3 times, respectively, more often than with PT - pic. 15.



Pic. 15 - The frequency of indicators "below the norm" in samples MVV25, MVV50, MVV75 in tuberculosis and sarcoidosis of the lungs (%).

The presented data indicate that in PT, ventilation respiratory failure, to a greater extent, pathogenetically develops according to a restrictive type, obviously due to fibrotic processes that affect the extensibility of the lungs.

In PS, predominantly, the development of ventilatory respiratory failure pathogenetically follows an obstructive type, with a violation of the passive exhalation function.

Three types of diffuse lung lesions are known: predominantly obstructive processes in the bronchopulmonary system, which are characterized by an increase in resistance to the passage of air due to partial or complete obstruction at any level (from the trachea to the respiratory bronchioles) and the loss of the ability to passively exhale; predominantly restrictive processes, in which the possibilities of expanding the lung parenchyma are reduced and the gas exchange surface is reduced during inspiration with a decrease in VC; in / mixed, when both

obstructive and restrictive lung lesions occur [Valiev R.Sh., Valiev N.R., 2017 Churilov L.P., 2017].

In PT and PS, mixed disorders were found equally often - in 35.8±6.6% and in 37.1±7.5% of patients, respectively (p>0.05) - Table 21.

Obstructive disorders in PS (45.2±7.7%) were found three times more often than in PT 15.1±4.9% (p<0.05), and restrictive disorders, on the contrary, were noted 3 times more often in PT (49.0±6.9%) than in PS (16.7±5.8%; (p<0.05).

In PT, total restrictive and mixed disorders in lung tissues were found in 84.8% of patients, while in PS, total obstructive and mixed disorders predominated, which were observed in 82.3% of patients.

Table 21 - The frequency of obstructive, restrictive and mixed pulmonary dysfunction in patients with tuberculosis and sarcoidosis of the lungs (M±m%)

	Group 1 (n=53)		Group 2 (n=42)	
Types	Abs.	M±м%	Abs.	M±м%
Obstructives	8	15,1±4,9	19	45,2±7,7#
Restrictives	2	49,0±6,9	7	16,7±5,8#
Mixed	19	35,8±6,6	16	37,1±7,5

Note: # - The difference in frequency indicators in the 1st and 2nd groups is significant (p<0.05).

The picture inherent in the group of patients with PT was obviously associated with the presence of patients with fibrous-cavernous and infiltrative forms of the disease, which change the extensibility of the lungs during inspiration and reduce the surface of gas exchange. This corresponds to the observations of a number of other authors [Muñoz-Torrico M. et al., 2016]. The trend we found towards an obstructive pattern of development of respiratory failure in PS would seem to contradict the classical reckoning of this disease to the range of restrictive parenchymal pulmonary disorders. But this is consistent with the data obtained in the last 15-20 years on the high frequency of airway lesions in sarcoidosis and the bronchoconstrictor effects of bioregulators produced in sarcoidosis granulomas.

Obstructive phenomena were found to be dominant in cohorts of sarcoid patients in many studies [Laohaburanakit P., Chan A., 2003; Morgenthau A.S., Teirstein A.S., 2011].

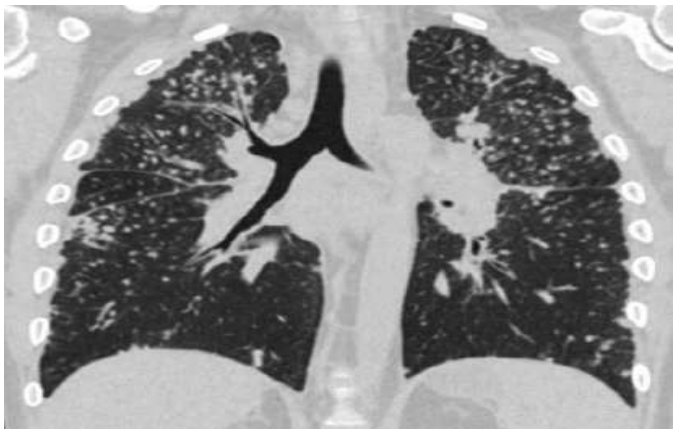
4.2 The results of radiation diagnostics of the state of the respiratory organs in patients with tuberculosis and sarcoidosis of the lungs

All patients underwent X-ray examinations (Table 22). It turned out that in both granulomatosis, certain signs of lung damage were equally common: in the 1st group in 49 people (92.5±3.5%), in the 2nd group in 40 patients (95.2±3.5%). .6%; p>0.05) - fig. 16-17. But the signs differed in their spectrum: in PS, 71.4±7.0% of patients had enlarged mediastinal lymph nodes, which was 3.4 times more common than in patients with PT (20.8±5.6%) with high degree of statistical significance (p<0.001). Ground glass syndrome was observed only in the group of patients with PS, in 7 people (16.7±5.8%) and was never observed in LT. At the same time, pleural effusion was detected by X-ray only in PT, in 7 patients (13.2±4.6%).

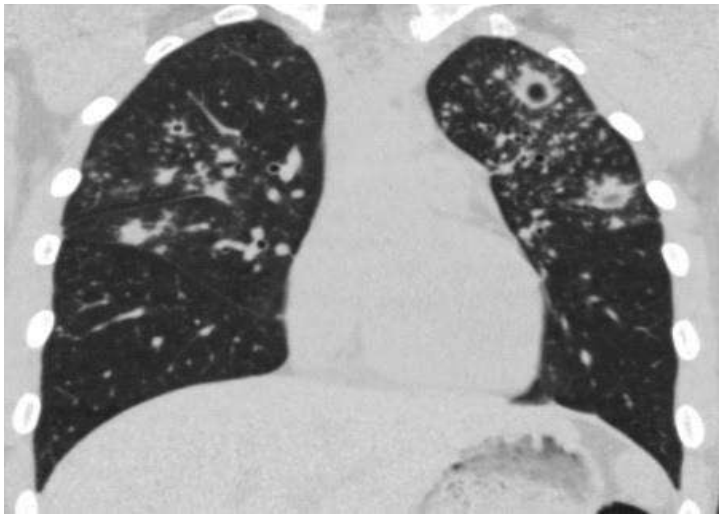
Table 22 - The frequency of pathological findings in lung radiography in patients with tuberculosis and sarcoidosis (M ± m %).

	Group 1 (n=53)		Group 2 (n=42)	
	Abs. M ±	Abs.	M±м % b	M±м%
Enlarged mediastinal lymph nodes	11	20,8±5,6	30	71,4±7,0#
frosted glass syndrome	-	0,0±0,0	7	16,7±5,8#
Single large foci	31	58,5±6,8	3	7,1±3,9#
Pleural effusion	7	13,2±4,6	-	0,0±0,0#
Total number of signs / per 1 person	49 / 0,92		40 / 0,96	

Note: # - differences in frequency between the 1st and 2nd groups of patients are significant ($p<0.05$-0.001).



Pic 16 - X-ray tomogram of the lungs in PS (own observation)



Pic. 17 - X-ray tomography of the lungs in PT (own observation)

The most frequently detected radiological sign in PT were single large lesions (in 58.5±6.8% of patients), while in patients with PS the frequency of their detection was significantly ($p<0.05$) lower and amounted to only 7.1 ±3.9%, which was 8.2 times less than in the PT group.

Thus, X-ray examination revealed lung pathology not in all examined patients with PT and PS (in the latter case, this happened somewhat more often), which coincided with the literature data [Karpov D.S., Konstantinova S.B., 2016].

The advantage of computed tomography (CT) over X-ray examination of the lungs is the ability to reduce the thickness of the tomographic layer to 0.5–1 mm when performing a spiral (continuous) scan and obtain more tomographic

sections, and, therefore, more detailed information about the state of the lung tissue [Marchiori E. et al., 2010].

As with lung radiography, the leading symptom in SL was mediastinal lymphadenopathy, which was noted in 95.2±3.4% of cases, 4.2 times more often than in PT (22.6±5.8%; p<0.001) – table23.

Table 23 - The frequency of detection of pathological manifestations of tuberculosis and sarcoidosis of the lungs during computed tomography (M ± m %).

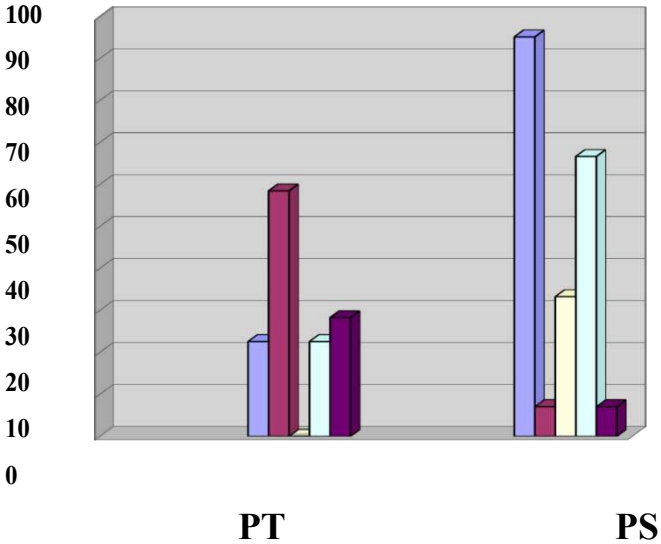
	Abs	M±м %	Abs	M±м %
Mediastinal lymphadenopathy	12	22,6±5,8	40	95,2±3,4*
Single large foci lung lesions	31	58,5±6,8	3	7,1±,3,9*
frosted glass syndrome	-	0,0±0,0	14	33,3±7,3*
Small-focal dissemination of lung tissue	12	22,6±5,8	28	66,7±7,3*
Consolidation Syndrome	-	0,0±0,0	3	7,1±3,9
Massive fibrosis of lung tissue	1	1,9±1,9	5	11,9±5,0
bronchiectasis	15	8,3±6,2	3	7,1±3,9*
Pleural effusion	6	11,3±4,3	2	4,8±3,4
Total features /per 1 person	77/1,5		98/2,3	

Note: *- differences in frequency indicators between the 1st and 2nd groups of patients are significant (p<0.05-0.001)

In PS, 3 times and 6.2 times more often (p>0.05-<0.05) than in the group of patients with PT, there were signs such as small-focal dissemination (66.7±7.3%) and massive fibrosis of lung tissue (11.9±5.0%).

Lymph nodes of the mediastinum had a spherical or ovoid shape, a homogeneous structure and smooth clear contours without perifocal infiltration and sclerosis. In a third of patients (33.3±7.3%) with PS, calcifications were found in the structure of the lymph nodes, which manifested themselves in the form of multiple, bilateral, monolithic, irregularly shaped calcareous inclusions located far from the bronchi in the center of the lymph nodes. This sign was regarded as a symptom of "frosted glass", the morphological substrate of which is a multitude of tiny lesions of lung tissue. The ground glass symptom was never found in PT (p <0.001). In 3 cases (7.1±3.9%), consolidation syndrome was noted, and only in the group of patients with PS.

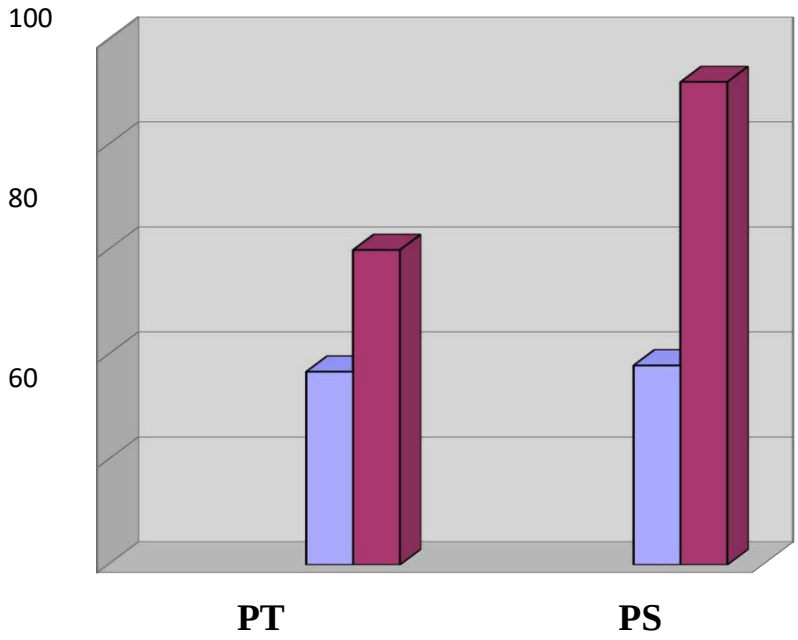
At the same time, single large foci, bronchiectasis and pleural effusion were detected significantly (p<0.05) in patients with PT, respectively, in 58.5±6.8%, 28.3±6.2% and 11.3% ±4.3% of cases, while in the group of patients with SL these signs were noted, respectively, only in 7.1±3.9%, 7.1±3.9 and 4.8±3.4%, respectively cases, that is, less often, respectively, by 8.2, 4.0 and 2.4 times - Pic. 18.



Pic. 18 - The frequency of the main CT signs of lung damage in PT and PS (%).

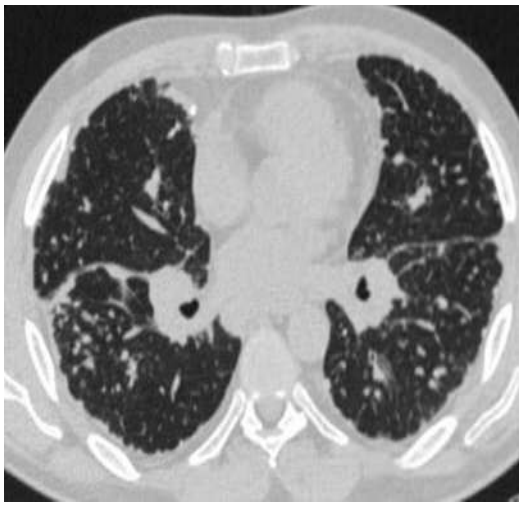
Note: order - lymphadenopathy, single large lesions, ground glass syndrome, small focal dissemination, bronchiectasis

CT showed not only a pronounced polymorphism of focal changes, but also a total greater number of signs of lung damage than on radiography (with PT - 77 signs in 53 patients - 1.5 per person; while with PS - 98 signs in 42 patients - 2.3 per person - Fig. 19), and the pathomorphological substrate of this was a multitude of tiny lesions of the lung tissue, which were located along the bronchovascular bundles, interlobar fissures, costal pleura, in the interlobular septa, causing uneven, "bead-like", thickening interstitial structures of the lungs - fig. 17. These data coincided with the literature data [Miranda E.J. et al., 2011].

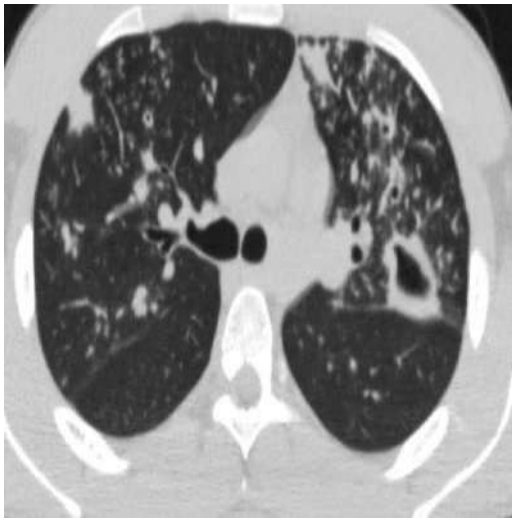


Pic.19 - The number of signs of lung damage on radiography and CT per 1 person with PT and PS (arb. units).

Thus, the most characteristic signs of lung damage on CT were: lymphadenopathy, small-focal dissemination of lung tissue, ground glass syndrome (more typical for PS), single large foci of lung lesions and bronchiectasis (more often observed in PT) - Fig. 20, 21.



Pic. 20 - Computed tomography in lung sarcoidosis (own observation)



Pic. 21 - Computed tomography in pulmonary tuberculosis (own observation)

Above, in Section 4.1, there was a discussion of the association of bronchoconstrictor bioregulators secreted by sarcoid granulomas and predominantly obstructive pulmonary dysfunction in SL, which confirmed bronchopulmonary involvement. In PT, it was noted, mainly, fibrosis and infiltrates. With radiation diagnostic methods, the PS picture was associated with such manifestations as lymphadenopathy, small-focal dissemination in the lung tissue, ground glass syndrome, which corresponded to the literature data [Baughman R.P. et al., 2012; Cottin V. Muller-Quernheim J. 2012; Nunes H. E5t

al., 2012]. Interestingly, some of these changes have recently been canceled out with a new coronavirus infection [Moazzam M. et al., 2020].

In general, with the help of radiation diagnostic methods in patients with PT and PS (Tables 23, 24, Fig. 16, 17), signs of lung damage were confirmed, which had their own characteristic features for each disease [Zimina V.N. et al., 2016; Fritscher-Ravens A. et al., 2011]; Reich, J.M., 2012; Spagnolo P. et al., 2012Santiago J.F., 2015].

CONCLUSION

So, in total, 53 patients with PL were examined (Group 1), 42 - with PS (Group 2), and 30 practically healthy people made up the control group.

According to the main anamnestic parameters (age, frequency of somatic pathology, smoking), the groups did not differ statistically significantly, they were comparable.

At the time of examination, the patients were in a compensated state, but patients with PT were characterized by complaints of cough, sputum expectoration, chest pain, hemoptysis (in 45.3±6.8%, 18.9±5.4%, 18 .9±5.4% and 7.6±3.7% of observations, respectively), which was 1.7, 3.9, 2.7, and 7.6 times more frequent, respectively ($p>0.05<0$, 05) than in PS patients. On the contrary, artalgia in PS was observed in 28.6±7.0% of patients, which was 7.5 times more common than in PT (in 3.8±2.7%; $p < 0.001$).

In PT, there were never complaints of myalgia, erythema nodosum, and the presence of complete Löfgren's syndrome, and in the group of patients with PS, these manifestations were noted in 4.8%, 7.1%, and 7.1% of cases, respectively ($p>0.05$) . In PT and PS, there was a relatively high frequency of complaints of weakness, malaise (in 30.2±6.3% and 42.9±7.6%, respectively; $p>0.05$), every third patient in the groups had an increase body temperature, irritability, sleep disturbance ($p>0.05$).

These complaints indirectly pointed to the syndrome of excessive systemic action of autocoids (ISDA) of a pro-inflammatory nature (“general intoxication”).

In terms of clinical blood analysis in PT and PS (to a lesser extent), in comparison with the data of healthy individuals, the average hematological parameters (except for the ESR) did not go beyond the generally accepted normal intervals, but the same unfavorable trend was noted: a significant drop in the average number erythrocytes, an increase in the number of leukocytes and an ESR index. With exacerbations of diseases, the analyzes worsened, the presence of the

ISDA syndrome in patients was also confirmed by the calculated indicators of LII and NII, respectively). In comparison with the data of the control group, the average indicators of LII according to J. Kalf-Kalif (1939) in the 1st and 2nd groups turned out to be significantly two times lower (by 0.4±0.02 units) due to the presence of eosinophils in the blood test. LII indicators according to A.L. Kostyuchenko-A.A. Sokolov in PT and PS also turned out to be the same, 0.97 ± 0.03 arb. units, significantly exceeded those in healthy donors (0.86±0.04; $p<0.05$).

The average quantitative values of the NII indicator (Dashtayants G.A., 1978) in the 1st, 2nd and control groups amounted to 0.09±0.003 arb. Unit, 0.07±0.003 arb. Unit and 0.02±0.005 arb. units accordingly, they were significantly higher in pulmonary patients, to a greater extent in PT ($p<0.05$). That is, the NII indicator is more accurate than the LII indicator (calf-Kali calculation gave a false-negative result), confirmed the presence of the ISDA syndrome (endotoxicosis according to outdated concepts) and was higher in PT. In the biochemical analysis of blood, the same pattern was noted: the average values of the indicators were within the generally accepted norm, but turned out to be significantly worse than in healthy individuals ($p<0.05$-0.001; the difference in blood sugar level was not significant). In the groups of pulmonary patients themselves, the average indicators were worse in patients with PT, but significantly only in terms of the level of C-reactive protein ($p<0.05$). This meant that, despite the presence of severe lung pathology and manifestations of ISDA, the homeostatic functions of the liver and kidneys in PT and PS were mainly preserved and the studied biochemical blood parameters had no diagnostic significance in patients with PT and PS in the compensated state, except for the level C-reactive protein.

The manifestations of ISDA in pulmonary patients were accompanied by immune changes characteristic of inflammation. Thus, activation of innate immunity was noted with a simultaneous decrease in the reserves of neutrophil function for the destruction of pathogens: 1 / average spontaneous and stimulated

NST tests in the control group were 12.4±1.2% and 21.1±1.3%, respectively ($p < 0.001$), significantly increased in PT up to 20.7±1.5% and 25.2±1.4%, respectively ($p<0.05$), in PS - up to 19.6±1.6% and 27. 1±1.3%, respectively ($p<0.001$) [Nikolaev A.N. et al., 2021].

The average stimulation index (SI - the ratio of stimulated to spontaneous NBT-test) in the control was 1.7 ± 0.06 units, in PT - 1.2 ± 0.04 units. units and with PS - 1.4±0.05 arb. units ($p<0.05$ compared to control), respectively. At the same time, in the groups of patients, the difference in the average values of spontaneous and induced NST was unreliable ($p>0.05$), and in terms of IS it was significant ($p<0.05$) [Nikolaev A.N. et al., 2021]..

The average content of lymphocytes in the blood in PT and PS was almost the same, amounting to 34.4±0.4% and 35.8±0.6%, significantly higher than in practically healthy people (31.2±0.3% ($p<0.05$).The relative mean content of CD3+T-lymphocytes in the peripheral blood in the 1st, 2nd groups of patients and in the control group was 74.6±7.3%, 79.1±3.6%, respectively. and 74.2±8.5%, i.e., slightly increased in pulmonary pathology ($p>0.05$).At the same time, the indicators of the relative average content of CD20+ B-lymphocytes in PT and PS were almost the same (12.8±0, 4%, 12.7±0.4%, respectively), but significantly higher than in healthy individuals - 11.7±0.3% ($p<0.05$) [Nikolaev A.N. et al., 2021].

The percentage of natural killers (NK cells) CD16+CD56+ in peripheral blood in the 1st and 2nd groups of patients was 13.4±0.8% and 11.0±0.9%, respectively, which was significantly higher ($p<0.05$) than in the control group (9.3±1.0 x103/μl). The indicators of the average relative content of T-helpers (CD4+,%) in PT and PS were significantly reduced (31.9±1.6% and 32.2±1.4%) compared with the data in healthy people (37.2± 1.7%; $p<0.05$). At the same time, the content of CD8+ in these groups had an inverse relationship, amounting to 20.4±1.8%, 15.9±1.1% and 15.3±1.0%, respectively. At the same time, the calculated average CD4/CD8 index in PT was 1.6±0.2 arb. Unit and significantly

differed from the indicator in PS - 2.0±0.1 arb. units and in healthy people - 2.4±0.2 arb. unit ($p<0.05$) [Nikolaev A.N. et al., 2021].

Thus, lymphocytoimmunograms had a unidirectional dynamics of the indicators of the relative content of immunocompetent cells in PT and PS (although in the latter case, the shifts were less pronounced). In PT, the most significant increase in the levels of NK-cells (killers), B-lymphocytes (CD20+) was noted with a decrease in the CD4+/CD8+ index, reflecting increased tissue destruction with an increase in the degree of ISDA and activation of the acute phase response against the background of the inflammatory process in the body, which corresponds to the data literature (Rakhmatullina I.R. and Valieva N.G., 2003; Churilov L.P., 2021).

Cytokines are responsible for such reactions, and it turned out that IL-2 levels were significantly reduced ($p<0.05$) in PT (38.8±7.9 pg/ml) and in PS (46.2±11.2 pg /ml; $p>0.05$ with the PT group), compared with the level in the control group (98.5±6.4 pg/ml). This fact indicates a violation of the differentiation of naive T helpers along the Th1 and Th2 pathways in both granulomatosis with an increase in the autoreactivity of the immune system of pulmonary patients. On the other hand, the average concentrations of IL-4 were significantly ($p<0.001$) increased in both PL and PS (not significantly different between groups of patients - $p>0.05$) compared with the corresponding indicator in the control group, amounted to 32.9 ±9.2 pg/ml, 41.3±7.2 pg/ml and 4.2±0.8 pg/ml, respectively. An increase in the level of IL-4 in pulmonary diseases apparently reflected the fibrous-cavernous stage of the process in PT, and in PS, the features of the formation of sarcoid granulomas.

The content of IL-6 in blood plasma in PT and PS was 6.0±1.3 and 18.7±3.8 pg/ml and pg/ml ($p<0.05$), respectively, which was higher in 1.9 and 5.7 times, respectively, than in healthy people (3.1 ± 0.4 pg/ml; $p<0.05$).

Activation of cellular immunity and ISDA manifested itself in a sharp increase in the systemic concentration of one of the most important mediators of "endotoxicosis" and cellular cytotoxicity [Churilov L.P., 2021] - TNF-α, the

average levels of which in the blood of patients with PT were slightly higher than in the group patients with PS - amounted to 114.2±11.3 pg/ml and 101.2±12.5 pg/ml ($p<0.05$), respectively, which was 27 (PT) and 24 (PS) times, respectively higher than in the control group - 4.3±1.2 pg/ml ($p<0.001$).

The mean blood level of IFN-γ in patients with LT was significantly higher than in PS patients (185.4±21.2 pg/ml and 146.7±11.3 pg/ml, respectively; $p<0.05$) and in both groups of patients, this indicator is 3.5 and 2.8 times higher than in healthy individuals (50.9±1.6 pg/ml; $p<0.001$).

It should be emphasized that the levels of IL-2 (inducer of T-regulators), IL-4 and IL-6 (inhibitor of differentiation of T-regulators) were 1.2, 1.3 and 3.1 times higher, respectively, in the group of patients with PS than with PT. The levels of TNF-a IFN-γ, on the contrary, were 1.1 and 1.3 times higher in the group of patients with PT. That is, in general, in accordance with the cytokine theory of R.S. Bone (1996) of the origin of MODS, the changes noted above in the clinic and analyzes reflected a “compensatory anti-inflammatory response” with manifestations of an imbalance in the pro-inflammatory link of cytokines.

Analysis of the results of humoral immunity parameters showed that in patients with PT and PS, in comparison with data in healthy people, there is an inhibition of the synthesis of antibodies of the Ig A class, activation of the synthesis of antibodies Ig M and Ig G, an increase in the formation of low molecular weight (nmm) CEC and medium molecular weight CEC (cmm). These changes were more pronounced in PT, but the difference in mean values in PS was significant ($p<0.05$) only in relation to the levels of Ig G and CEC sm. These data confirm the fact of an increase in the levels of autoantigens in ISDA in pulmonary patients with damage to the lung tissue with activation of cellular immunity, which is more pronounced in PT.

In general, the ELI-test parameters in patients with PT and PS, the profiles of their autoimmune reactivity differed significantly, with the polar dynamics of a number of indicators, although there were also unidirectional shifts. At the same time, in the group of patients with PT, the values of the studied indicators with the

“+” sign, in comparison with the norm, were in 10 samples (values of + 30% or more - in 6 out of 10 tests, in the levels of AAT to β1-adrenergic receptors, to KiM-05 and others), with a "-" sign - in 14 samples (values -20% or less - in 9 out of 14 tests, in the levels of AAT to ds-DNA, to β2-glycoprotein I, etc.). There were 15 samples in PS with the “+” sign, + 27.8% was in one sample (AT to MBP), the other tests were at significantly lower values); with the sign "-" there were 9 samples (values -20% or less - with three samples, in the levels of AAT to KiM-05, to AdrM-D/C-0 and to insulin receptors). These data indicate a mosaic pattern of damage in the body in ISDA in patients with PT and PS and the actual multiorganism of processes with the presence of an autoimmune component, which is more pronounced in PS. At the same time, the average indicators of the total overall individual autoimmune reactivity of the body, assessed in the ELI test, in the group of patients with PT were 1.6 lower than those with PS (-43.7±5.2% and -27.0±3.7 %, respectively; $p<0.05$). And the average levels of AAT to lung tissues in PS were slightly higher than average levels, and in PT they dropped significantly, which can be associated either with the success of the therapy or with the "paradox of the body's immune response" to MBT with simultaneous activation and anergy of immunocompetent cells [Tang Y. , Stratton C.W., 2018].

In terms of the frequency of endocrine pathology (diabetes mellitus, diseases of the reproductive system, thyroid gland), the groups of patients with PT and PS were comparable ($p> 0.05$), but the study of the hormonal profile showed some features: and PS, the average concentration of this homeostasis ingredient was 2.3±0.3 ng/ml and 1.1±0.1 ng/ml ($p<0.05$), respectively, confirming the presence of ISDA in pulmonary patients, more pronounced in PT. For the first time in world practice, hyperprocalcitoninemia, which we have identified in PS, may have a neuroendocrine origin, as a compensatory reaction of the body against calcium metabolism disorders.

The mean cortisol level in patients with PT (942.3±36.5 nmol/l) was higher than in patients with PS (895.4±42.6 nmol/l; $p>0.05$), and both indicators were

significantly higher (by 1.7 and 1.6 times, respectively) than in practically healthy people - 543.2±45.5 nmol/l ($p<0.001$). This fact of hypercortisolism, which is more pronounced in PL, is apparently the result of a protective restraining effect of stress mechanisms on the potentially shockogenic response of the acute phase of ISAD (Churilov L.P., 2021).

The average concentration of T3 in the groups of patients with PT and SP was almost the same (1.3±0.1 nmol/l and 1.2±0.1 nmol/l, respectively; $p>0.05$), but in both groups it was significantly lower, than in the control group (1.7±0.1 nmol/l; ($p<0.05$). This fact is regarded by us as a manifestation of the "low triiodothyronine" syndrome, characteristic of cachectic autoimmune conditions (both infectious and non-infectious etiology) and ISDA Similar changes were observed in the study of T4 in the blood: in TP, PS, it averaged 78.2±4.6 nmol/l, 67.2±8.2 nmol/l ($p>0.05$), respectively, in both groups was significantly ($p<0.05$) lower than in the control - 97.0±1.7 nmol/l.

Mean TSH levels in the groups of patients with PT and PS were 4.7±0.7 and 3.6±0.5 nmol/l, respectively ($p>0.05$) and were significantly ($p<0.05$) higher than in the control group - 2.2 ± 0.6 nmol/l, which could indicate that euthyroidism in the pulmonary groups was maintained at the cost of greater tension in the compensatory hypothalamic-pituitary mechanisms. The same pattern was observed in terms of mean levels of prolactin in blood plasma in patients with PT was not significantly higher than in patients with PS - they amounted to 11.2±2.5 ng/ml and 9.5±1.7 ng/ml, respectively ($p>0.05$), in both groups of patients were significantly higher than in the control group (6.9±1.3 ng/ml; $p<0.05$). An increase in the level of the hormone in the blood in ISDA in patients with PT and PS was apparently associated with cytokinemia, a tendency to subclinical hypothyroidism, an autoimmune component in the pathogenesis of granulomatous diseases [Churilov L.P., 2017; Borba V.V. et al., 2018].

In all groups of patients, the average level of the inactive form of vttamin D (25 (OH) D) in blood plasma was below the generally accepted norm (20ng / ml), even in healthy people (19.3 ± 1.6 ng / ml), significantly decreased with PT

(9.8 ± 1.3; $p < 0.001$) and in PS (13.2 ± 1.5; $p < 0.05$). We attribute this phenomenon of hypovitaminosis D even in healthy people to the fact that blood was taken for analysis from April to June, when insolation in the area of St. Petersburg is still relatively low. At the same time, the average levels of the active form of vitamin D in blood plasma, in comparison with the indicators of the inactive form, increased ($p < 0.001$) in the control group by 1.9 times (35.5 ± 1.9 pg / ml), with PT - by 3 .7 times (36.4 ± 1.4 pg/ml). in PS - by 3.8 times (50.4 ± 1.6 pg / ml). It can be seen that in PT and in healthy people this indicator was almost the same, and in PS it was significantly higher than in PT and in healthy people ($p < 0.001$).

Activation of vitamin D was accompanied by an increase in the average concentration of the antimicrobial peptide LL-37 (catelicidin) in the blood plasma, which was: in the control group - 39.8 ± 2.1 ng/ml, in PT - 47.1 ± 2.2 ng/ml , with PS - 39.8 ± 1.6 ng/ml. That is, the concentration of cathelicidin was significantly increased in LT, in comparison with the data in PS and in healthy people ($p < 0.05$), which coincided with the data of A.A. Yamshchikov et al. (2010), who linked the compensatory synthesis of calecitidine with vitamin D deficiency.

The above changes in the hormonal status, the difference in the levels of inactive and active forms of vitamin D and cathelicidin indicate a significant metabolic response of the body of patients with PT and PS (to a lesser extent), aimed at providing a protective inflammatory response of the body with ISDA due to intoxication during destructive pathological processes in the lungs. .

When examining the function of external respiration according to the main indicators (VC, FVC, FEV1, Tiffno index, MVV25, MVV50 and MVV75), three features were identified:

1. Volumetric indicators of the function of external respiration were more often reduced in PT, and this was less typical for PS.

2. The Tiffno index "below normal" was detected in every fourth patient with PS, which was 3.3 times more often than with PT.

3. Among the indicators MVV25, MVV50 and MVV75, reflecting the patency of the bronchial system, "below the norm" in PS occurred in 20.9%, 29.2% and 45.8% of cases, which was in 1.6, 2 ,2 and 3 times more often, respectively, than with PT.

These data indicate that in PT, ventilation respiratory failure develops more of a restrictive type, apparently due to fibrotic processes that affect lung compliance. In PS, the development of obstructive ventilatory respiratory failure occurs predominantly, with a violation of the passive exhalation function.

In general, in PT, total restrictive and mixed disorders in lung tissues were found in 84.8% of patients, which, apparently, was associated with fibrous-cavernous and infiltrative forms of the disease. In PS, total obstructive and mixed disorders prevailed, they were noted in 82.3% of patients, which, apparently, was due to the high incidence of airway lesions and bronchoconstrictor effects of bioregulators produced in sarcoidosis granulomas.

An X-ray examination showed that in both granulomatosis, the signs of the total presence of signs of lung damage in the 1st group were in 49 people (per person - 0.92; 92.5±3.5%), in the 2nd group - in 40 patients (0.95 per person; 95.2±3.6%; $p>0.05$), i.e. more unreliably. But these signs differed in spectrum: in PS, 71.4±7.0% of patients had enlarged mediastinal lymph nodes, which was 3.4 times more common than in patients with PT (20.8±5.6%; $p< 0.001$). Ground glass syndrome was observed only in the group of patients with PS, in 7 people (16.7±5.8%) and was never observed in LT. At the same time, pleural effusion was detected by X-ray only in TL, in 7 patients (13.2±4.6%). The most frequently detected radiological sign in PT were single large lesions (in 58.5±6.8% of patients), while in patients with PS the frequency of their detection was 8.2 times less (7.1±3.9% $p<0.05$).

As with lung radiography, the leading symptom in PS was mediastinal lymphadenopathy in CT, which was noted in 95.2±3.4% of cases, 4.2 times more often than in PT (22.6±5.8%; $p< 0.001$). In PS, 3 times and 6.2 times more often ($p>0.05$-<0.05) than in the group of patients with PT, there were signs such as,

respectively, small-focal dissemination (66.7±7.3%) and massive fibrosis of lung tissue (11.9±5.0%). Lymph nodes of the mediastinum had a spherical or ovoid shape, a homogeneous structure and smooth clear contours without perifocal infiltration and sclerosis. In a third of patients (33.3±7.3%) with PS, calcifications were found in the structure of the lymph nodes, which manifested themselves in the form of multiple, bilateral, monolithic, irregularly shaped calcareous inclusions located far from the bronchi in the center of the lymph nodes. This sign was regarded as a symptom of "frosted glass", the morphological substrate of which is a multitude of tiny lesions of lung tissue. The ground glass symptom was never found in PT ($p < 0.001$).

Consolidation syndrome was noted in 3 cases (7.1±3.9%), only in the group of patients with PS. At the same time, single large foci, bronchiectasis and pleural effusion were detected significantly ($p<0.05$) in patients with PT, respectively, in 58.5±6.8%, 28.3±6.2% and 11.3% ±4.3% of cases, while in the group of patients with PS these signs were noted, respectively, only in 7.1±3.9%, 7.1±3.9 and 4.8±3±4% of patients , that is, less often by 8.2, 4.0 and 2.4 times, respectively.

Thus, the most characteristic signs of lung damage on CT were: lymphadenopathy, small-focal dissemination of lung tissue, ground glass syndrome (more typical for PS), single large foci of lung lesions and bronchiectasis (more often observed in PT).

CT showed not only a pronounced polymorphism of focal changes, but also a total greater than with X-ray, signs of lung damage (with PT - 77 signs in 53 patients - 1.5 per person; with PS - 98 signs in 42 patients - 2.3 per person). human), and the morphological substrate of this phenomenon was a multitude of tiny lesions of the lung tissue, which were located along the bronchovascular bundles, interlobar fissures, costal pleura, in the interlobular septa, causing uneven, "clearly" thickening of the interstitial structures of the lungs.

In any case, functional tests and radiological diagnostic methods confirmed the presence of morphological substrates in ISDA in PT (mainly restrictive and

mixed dysfunctions in fibrosis and infiltrates of the lung tissue) and PS (mainly obstructive and mixed dysfunctions in bronchopulmonary involvement).

CONCLUSIONS

1. Due to damage to body tissues in PT and PS (to a lesser extent) due to the accumulation of autakoids, the ISDA syndrome develops with a tendency to anemia, changes in the hemogram according to the type of acute phase response, an increase in leukocyte and nuclear indices of intoxication,

2. In the course of the neuroendocrine response of the body, an increase in the plasma concentration of cortisol, hyperprolactinemia and an increase in the level of TSH develop.

3. In PT and PS, hyperprocalcitoninemia is formed (and for PS this was revealed for the first time)

4. In PT and PS (to a lesser extent), protective activation of innate immunity (an increase in the levels of the NBT-test with a decrease in the reserve bactericidal capabilities of granulocytes), as well as adaptive cellular immunity (an increase in the total number of lymphocytes, T-, B-lymphocytes, natural killers) is detected in the blood, with a decrease in the proportion of T-helpers, the ratio of CD4+ / CD8+) and humoral immunity (inhibition of the synthesis of antibodies of the Ig A class with an increase in the synthesis of antibodies of Ig M and Ig G with an increase in the formation of the CEC with an imbalance in the spectrum of pro-inflammatory and anti-inflammatory cytokines).

5. Hypovitaminosis D was detected (to a greater extent in PT), which was compensated by an increased level of its activated form (calcitriol, to a greater extent in PS), and vitamin D associated antimicrobial peptide cathelicidin (to a greater extent in PT).

6. Signs of activation of autoimmunity were revealed in both granulomatosis, mainly in PS: in PT - in relation to 10, and in PS in relation to 15 of the 24 autoantigens tested. At the same time, the level of pulmotropic autoantibodies in PT is lowered, and in SP, on the contrary, it is increased.

7. According to the data of functional tests and radiological diagnostic methods, the main target and pathomorphological substrate in PT is the lung tissue, and in PS, the respiratory tract: PT is characterized by predominantly restrictive and mixed dysfunctions against the background of fibrosis and large foci of infiltration in the lung tissue, while while PS is characterized mainly by obstructive and mixed dysfunctions against the background of mediastinal lymphadenopathy and many tiny foci of lung tissue damage.

PRACTICAL RECOMMENDATIONS

The problem of differential diagnosis of PT and PS is hampered by the fact that most patients do not complain about the respiratory system and are in a stably compensated state for a long time.

Nevertheless, the completed complex scope of research allows us to offer the following algorithm for the actions of specialists:

1. At the first stage, measures are taken to exclude TH (fluorography, Mantoux reaction, etc.):

2. When analyzing clinical and biochemical blood tests, attention should be paid to identifying, including with the help of calculated indicators (LII, etc.), the nonspecific syndromes of PT and PS noted by us - accumulation of autocoids and a protective inflammatory response (anemia, leukocytosis, increased ESR etc.), protective tension of the functions of natural detoxification organs (OED - liver, kidneys);

3. It is necessary to perform immunograms with an assessment of non-specific (NST-test spontaneous and induced, secretion index) immunity, analysis of indicators of cellular immunity (T-lymphocytes, B-lymphocytes, helpers, cytotoxic cells, killer cells with calculation of the CD4 / CD8 ratio) and humoral immunity with the study of blood levels of Ig A, Ig A, Ig G and CEC nmm, CEC smm;

4. To clarify the degree of tension in the immune system, an ELI test should be performed, which allows you to determine the target organs and the implementation of the body's immune response (in PT - blockade of the production of AAT to lung tissue antigens against the background of deep damage in some other systems, in PS - confirmation of autoimmune, milder, but widespread damage to many organs and systems, including the lungs);

5. Instrumental studies with the study of spirograms are needed to clarify the nature of lung damage (in PT, predominantly rhythmic-mixed, in PS, predominantly obstructive-mixed) and their functional state;

6. Radiation diagnostic methods in the form of radiography and CT should be included in the "gold standard" for the study of patients with PT and SPL.

The results of the conducted studies allow us to guide doctors to correct vitamin D deficiency and conduct plasmapheresis, which has detoxifying, anti-inflammatory, rheo-, immunocorrective and other positive effects with prosthetics of the body's OED functions. Given the impact of these procedures on many links in the pathogenesis of PT and PS, plasmapheresis should be recommended to patients with recurrent course with concomitant diseases of AED (liver, kidneys, etc.), with poor tolerance to basic drugs. The latter is very important in MBT-resistant PT, and in PS, the maximum effect should be expected when plasmapheresis is combined with extracorporeal pharmacotherapy with corticosteroids.

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