UDC: 616.24-002.54

The study of the prognostic value of procalcitonin and changes in the blood coagulation system in the course of pulmonary tuberculosis.

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Resume. The article deals with scientific papers from 183 sources, of which 119 (65%) belong to the authors of the CIS countries, 64 (35%) - to the authors of the far abroad. The results of the analysis showed that the literature devoted to solving the complex problem of changes in the procalcitonin and blood coagulation systems in the destructive form of pulmonary tuberculosis is very rare, which requires research in this area.

Key words: destructive tuberculosis, infiltrative tuberculosis, cavernous tuberculosis, fibrous-cavernous tuberculosis, cirrhotic pulmonary tuberculosis, epidemiology, diagnosis and differential diagnosis, treatment, procalcitonin, d-dimer, fibrinogen.

Introduction. Tuberculosis is an infectious disease caused by mycobacteria of the M. tuberculosis complex, and the causative agent is M. tuberculosis, M. africanum, M. microti, M. canetti, M. pinnipedii, M. caprae, M. Bovis. there is. The morphological basis of the disease is inflammation, characterized by the formation of granulomas with the presence of epithelioid and giant cells of the Pirogov-Langhans type, which may develop caseous necrosis. For the primary infection of a person with Mycobacterium tuberculosis (TMB), the aerogenous mechanism of infection is the most characteristic, less often, the infection occurs in the alimentary or vertical way [72, 50, 14].

Mycobacterium tuberculosis belongs to the genus Procaryotae. Their nucleus is shellless, composed of nuclear and basic proteins (histones), and their cytoplasm does not have perfected organelles (mitochondria, Golgi apparatus, lysosome). TMB are slightly curved or straight rods, 1–10 μm long and 0.2–0.6 μm wide, with rounded tips. They are usually long and thin, but the cattle type trigger is relatively thick and short. Mycobacteria are inactive, endospores and capsules are not formed. A bacterial cell has a microcapsule with a thickness of 200-250 nm, consisting of a 3-4-layer wall, cytoplasm, cytoplasmic membrane and a nuclear substance - a nucleotide [49].

Forms of tuberculosis with a destructive form of the lungs include: the decay period of tuberculosis with infiltrative and dissemination, cavernous,

fibro-cavernous, cirrhotic pulmonary tuberculosis [61]

Epidemiological features

Tuberculosis has been a global health problem for many decades due to its high prevalence, duration, susceptibility to complications and chronicity of the process, as well as insufficient treatment efficiency [16, 59, 110].

Despite the improvement trend of some indicators noted by a number of experts, the epidemic situation of tuberculosis remains acute in a number of countries and regions [89, 87, 62, 109, 132, 135]. According to statistics, the majority of tuberculosis patients are currently in South Africa (26.2%), Southeast Asia (45.6%), Eastern Mediterranean (7.2%), European and American regions (3.1%) live in their countries. According to WHO documents, tuberculosis is one of the 10 leading causes of death in the world, ahead of both HIV infection and malaria. In 2016, 1.8 million people died from this disease (including 0.4 million people with HIV infection) [157].

A total of 1.4 million people died of tuberculosis in 2019 (including 208,000 people living with HIV). Worldwide, tuberculosis is one of the 10 leading causes of death and the leading cause of death associated with any infectious disease (surpassing HIV/AIDS). An estimated 10 million people worldwide were infected with tuberculosis in 2019, including 5.6 million men, 3.2 million women and 1.2 million children. Tuberculosis is common in all countries and age groups. Multidrug-resistant tuberculosis (MDR-TB) remains a threat to public health. A total of 206,030 people with multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB) were diagnosed and registered in 2019, which is 10 percent more than in 2018 (186,883 people). Currently, one of the most difficult problems of phthisiology is the increase in tuberculosis caused by drug-resistant strains of mycobacteria. WHO estimates that 558,000 people worldwide were infected with rifampicin-resistant TB in 2017, 82% of whom had multidrug-resistant TB. Almost half of the cases of drug-resistant tuberculosis occur in three countries: India (24%), China (13%), and the Russian Federation (10%).[2, 178]. Current treatment regimens for MDR and XDR TB are significantly less effective and more toxic than those used to treat drug-susceptible TB [25, 130, 140].

In 2013, the effectiveness of treatment of patients with MDR MBT in the Russian Federation was 38.1%, with XDR MBT - 26.2% [92] and according to world statistics, 52% of patients with MDR MBT and only 28% of patients with XDR MBT completed a successful course of treatment [16, 25].

In subsequent years, treatment success rates were slightly higher, reaching 64% in patients with MDR, and 40% in patients with mycobacteria resistant to fluoroquinolones and reserve line injectable drugs [15, 17, 65, 136, 154].

In patients with drug-resistant tuberculosis, the use of more aggressive individualized regimens does not significantly increase the effectiveness of treatment and leads to increased side effects and ultimately discontinuation of anti-tuberculosis treatment [7]. The development of adverse drug reactions in patients is an important factor that reduces the frequency of abstinence [7, 108, 112, 116, 155]. Poor tolerance of anti-tuberculosis therapy forces patients to

refuse to take drugs, which leads to further development of the disease, contributes to the expansion of the spectrum of DR MBT, and also complicates the use of surgical methods of treatment, making the treatment of such a patient very difficult.[21, 38, 146, 182].

Among the newly diagnosed active tuberculosis diseases, respiratory tuberculosis is the majority - 96-97% [96]. At the same time, infiltrative pulmonary tuberculosis is the most common form of pulmonary tuberculosis, its share in pulmonary forms of tuberculosis is about 60-85% [93]. The development of infiltrative pulmonary tuberculosis is based on the exudative-pneumonic process, which develops as a perifocal inflammation in the process of new growth or as a result of an increase in old caseous, encapsulated, calcified foci and fibrofocal changes [93]. More than 60% of infiltrative pulmonary tuberculosis is accompanied by destruction and release of bacteria, which often increases the risk of developing chronic forms of tuberculosis that require surgical treatment [29, 74].

Fibrous-cavernous tuberculosis of the lung is one of the most severe paralysis of tuberculosis, and the mortality rate is observed in at least 40% of cases and takes the leading place [19, 46, 66, 139].

Pathogenesis of pulmonary tuberculosis

The development of infiltrative tuberculosis is associated with the development of endogenous reinfection focal tuberculosis disease - the appearance and increase of the infiltration zone around new or old tuberculosis foci. Intensification of inflammation is caused by massive tuberculosis superinfection, concomitant diseases (diabetes, alcoholism, drug addiction, HIV infection), as well as hunger, psycho-emotional trauma, natural hormonal restructuring, the use of hormonal drugs in large quantities, cytostatics and immunosuppressive therapy. cause. These important factors reduce the effectiveness of immune responses and create the necessary conditions for the growth and reproduction of mycobacteria. As a result, an inflammatory reaction with a pronounced exudative component appears around the focus of tuberculosis . Specific inflammation spreads outside the lung lobe - a broncholobular infiltrate appears. Further development is characterized by an increase in the level of damage. Formed infiltrates differ in developmental characteristics, but these differences mostly disappear over time. With a relatively moderate increase in the population of mycobacteria and an increase in the sensitivity of tissues to mycobacteria, the reaction of perifocal tissues has an exudative-proliferative nature. In such conditions, a round infiltrate is formed in the affected segment. A sharp increase in the hyperergic reaction to the rapidly growing population of lung tissue leads to a significant increase in exudation and the involvement of adjacent segments in the pathological process. A cloud-like infiltrate is formed in this way. Then the increase of caseous-necrotic tissue reaction, dissolution and release of caseous masses through the draining bronchus leads to the formation of cavities. There are conditions for massive bronchogenic spread of mycobacteria, which leads to the appearance of new foci and infiltrates. Involvement of the entire lobe of the lung in the process and the appearance of several cavities in it indicates the formation of a lobit. Infiltrates are often localized in the I, II

and VI segments of the lungs, that is, in the sections where the foci of tuberculosis patients are located. According to the localization and degree of damage, broncholobular infiltrate is distinguished, usually includes 2-3 lung lobes, segmental - within one segment, as well as polysegmental or lobar infiltrate, infiltration located along the interlobar fissure perisissuritis is called caseous pneumonia and cavernous tuberculosis develop if infiltrative tuberculosis is not treated. Sometimes the infiltrate turns into a tuberculoma. Regression of infiltrative tuberculosis against the background of treatment is characterized by resorption of inflammatory processes, development of fibrosis, absorption and encapsulation of caseous masses. A fibrous focus gradually forms at the site of the caseous cavity, and as a result of fibrous tissue growth, a linear or star-shaped scar may appear [73].

Pathogenetically, the destructive form of tuberculosis infection often develops from infiltrative pulmonary tuberculosis, less disseminated and focal pulmonary tuberculosis [55, 58]. Fibrosis-cavernous tuberculosis is the final stage of the progressive process of destructive pulmonary tuberculosis disease [69]. Regardless of the variety of clinical and pathomorphological characteristics of fibro-cavernous tuberculosis, the presence of a fibro-cavernous space is a mandatory morphological component, that is, cavities, damage to vessels and clear fibrotic changes in the surrounding lung tissue [1, 4, 105].

The formation of destruction in the lungs is a very important and often critical stage in the clinical presentation, period and outcome of the disease. Fibrosis-cavernous tuberculosis and its complications are the main cause of death of 75-80% of patients with pulmonary tuberculosis [33]. Disintegration of a specific inflammatory focus in the lungs and the appearance of a cavity can develop in any form of tuberculosis, for which there is a change in the body's reactivity, in its sensitization, in massive superinfection, in the presence of other diseases. can be observed in the case of swelling and under the influence of various harmful factors that reduce the overall resistance. Under the influence of these factors, the permeability of blood vessel walls increases in the area of inflammation, the proliferation of mycobacteria increases. Granulation tissue, caseous masses, polynuclear cells secreting lymphoid elements and proteolytic enzymes are infiltrated in the area of damage, and a perifocal inflammatory zone appears around it. Later , destruction is formed as a result of necrobiosis and purulent masses . It remains closed for some time, then its contents are drained through the bronchus and atmospheric air enters the empty space, creating a destruction cavity. The wall of the newly formed fragmentation cavity consists primarily of two layers: the inner - pyogenic necrotic and the outer - granulation layer. Later, collagen fibers are gradually formed in the outer part of the granulation layer, which form a thin fibrous layer. Over time, a three-layer wall characteristic of the cavity is formed around the decay cavity. The size of the gap varies from a few millimeters to 10-20 cm. Medium (from 2 to 4 cm) cavities are more common, less large (4-6 cm) and giant (more than 6 cm) cavities are found. The size of the cavities depends not only on the size of the destroyed lung tissue, the elasticity of the parenchyma around it, and the condition of the draining bronchi, which are often involved in the

pathological process. With the development of the process, the bronchial walls are infiltrated with lymphoid and epithelioid cells, the mucous membrane is replaced by specific granulations, scars appear, which leads to the formation of various degrees of stenosis. As a result, the normal permeability of the bronchi is disturbed. In such cases, its dimensions often significantly exceed the actual size of the destroyed lung tissue, and an atelectasis or dystelectasis zone is formed around the cavity [33].

The cavernous body is a receptacle for an unstable, ever-expanding population of tuberculosis, which is characterized by pronounced inflammation and necrobiotic processes in the wall of this cavity [82, 102]. The spread of the pathological process outside the reservoir occurs by bronchogenic spread and can cover a large part of the lungs. In addition to the appearance of new cavities, other morphological changes occur, characterized by sclerotic and destructive processes, which lead to a significant decrease in functionally active lung tissue [33, 86].

In particular, pneumosclerosis is a morphological expression of lung regenerative processes and is a non-specific result of many chronic diseases. Pneumosclerosis is characterized by the growth of granulation tissue and subsequent fibrous transformation [95, 127]. In pneumosclerosis, all structural elements of the lungs are affected: alveoli, interstitial space, bronchi, blood and lymph vessels, nerves [162, 166].

Many authors, including Erokhin V.V. suggest the ambiguous role of intercellular interactions of alveolocytes, macrophages, endothelium, fibroblasts and transient leukocytes, bronchial epithelium and smooth muscle cells, as well as neuroendocrine cells in the formation of the fibrous cavity and pneumosis. . [27, 28, 152].

To date, the functional state and interaction of organ parenchyma and connective tissue influence exudative and proliferative processes, including the reparative regeneration of damaged components [141]. At the same time, the metabolic products of the connective tissue itself and its cellular structures can stimulate the proliferative activity of parenchymal elements and negatively affect the processes of organotypic regeneration [160]. There is very little information about the relationship between the activity of fibroblasts, lymphoid cells and macrophages , which affects the intensity of sclerotic processes [183]. The formation of a large number of lymphoid follicles and defective thin-walled capillary vessels is accompanied by the activation of fibroblasts, which is an unfavorable factor leading to fibrosis and cirrhosis, which reduces the effectiveness of the treatment of destructive forms of tuberculosis [58].

One of the leading roles in the implementation of immune protection of the lungs is macrophages. In inflammation, macrophages have three main functions; Antigen function, phagocytosis and immunomodulation through the production of various cytokines and growth factors. Macrophages play an important role in the initiation, maintenance and resolution of inflammation [143]. They are activated and deactivated during inflammation . Activation signals include cytokines (interferon gamma, monocyte granulocyte colony-stimulating factor , and TNF-alpha), bacterial lipopolysaccharide, extracellular matrix proteins, and other

chemical mediators [153]. Inactivation of inflammation by inhibiting inflammatory mediators and effector cells allows repair of damaged tissues. Activated macrophages are mainly inhibited by macrophage-produced anti-inflammatory cytokines (IL-10 and TGF-beta) and cytokine antagonists. During inflammation, macrophages participate in the autoregulatory loop [144]. Macrophages produce a wide range of biologically active molecules that have positive and negative consequences during the inflammatory process, including intercellular interactions before the formation of granulation tissue [120].

The combination of sequential processes of inflammation, regeneration and fibrosis is determined by the macrophage-fibroblast interaction that determines the development, formation and reduction of connective tissue [137, 142]. This regulatory function is performed by collagen degradation products that activate macrophage chemotaxis mechanisms. In turn, macrophages phagocytize degradation products, which leads to their activation and, accordingly, stimulation of fibroblast proliferation with subsequent collagen synthesis [154, 158].

Macrophage-fibroblast interaction and the growth of "imperfect" vessels have an enhancing effect on the migration and proliferation of fibroblast cells, leading to an increase in the migration and proliferative activity of fibroblasts and the activation of their differentiation. In turn, fibroblasts play a leading role in the production of extracellular matrix components, such as various types of collagen and fibronectin, and consequently in active fibrillogenesis [43, 104]. Embryonic lung tissue is dominated by type III collagen, which allows us to interpret it as the most complementary stromal element in terms of lung tissue formation and growth. Collagen types IV and V are characterized as difficult-to-degrade proteins that can only be cleaved by type IV collagenase, which is not detected in lung tissue or in components of the inflammatory infiltrate [156, 156]. The presence of a non-degradable fibrous tissue matrix may contribute to the molecular genetic rearrangement and transformation of the lung epithelium , which is a prerequisite for the development of lung cancer in the background of fibro-cavernous tuberculosis [15, 166].

Diagnostics and differential diagnosis

In the Russian Federation, great importance is attached to the detection of pulmonary tuberculosis through preventive fluorographic examination of the population, which often allows to detect tuberculosis at an early stage [9, 60]. Low coverage of the population with prophylactic fluorography and violations of its rules, especially in the group of incorrectly formed contingents, cause late detection of the processes with destruction cavities and bacterial separation in primary patients [39].

Patients with complaints of a bronchopulmonary nature and obvious changes in the chest organs on X-ray are referred to general medical network institutions, which in turn requires a quick differential diagnosis to prescribe the correct therapy [39].

There is no information on the structure of the changes in the lungs detected by X-ray examination in the official statistical reports. At the same time, some scientists pay attention to the fact that mainly infiltrative changes are

detected in the lung tissue during X-ray examination [79]. Thus, NAKatorgin and VAStakhanov state that during the patient's initial visit to the doctor, infiltrative processes in the lungs were detected in 66.3% of cases, according to NIRubleva and FRIsmoilova et al., in 46% and 43% of cases, respectively. [31, 36, 85].

In addition, immunological methods such as diaskintest® recombinant tuberculosis allergen test, quantiferon test (QuantiFERON TB Gold) have recently been widely used in the diagnosis of tuberculosis, which, according to the literature, can increase the effectiveness of the diagnosis and treatment of tuberculosis. [91, 30].

Early detection of pulmonary tuberculosis is one of the priorities of anti-tuberculosis institutions. If typical changes in the lung tissue are detected, patients are sent to anti-tuberculosis institutions to rule out the local form of tuberculosis, where the base of clinical, laboratory, instrumental and X-ray methods allows for complex diagnostic studies. There are certain algorithms for the diagnosis of pulmonary tuberculosis, which allow to verify the diagnosis [78, 115]. At the same time, due to the modernization of diagnostic methods and the pathomorphism of respiratory diseases, the diagnostic algorithm does not take into account all modern methods, the use of which reduces the time of diagnosis [26, 115].

The X-ray method is mainly used to determine the destroyed space in the lungs. the main radiographic symptom of a destroyed space is the presence of an annular shadow around the space with a continuous closed contour that continues in at least two mutually perpendicular projections. In addition to the main X-ray sign of a destroyed tuberculosis cavity in the lungs, additional X-ray symptoms may be detected:

- the presence of a horizontal or meniscus-shaped level of fluid in the lung tissue;
- signs of the draining bronchus, which are visible as a result of infiltration or sclerosis of its walls and are aimed at the location of the cavity in the lungs as an indicator;
- in some cases, in the absence of a clear X-ray image of the cavity, foci of bronchogenic proliferation are detected, which indirectly indicates its presence. They are usually large, irregular in shape, without a clear contour, numerous and have a typical localization in the lungs. Such foci are located below the source of their origin and in greater numbers in the anterior (3, 4, 5) and lower (7, 8, 9, 10) segments, which are well ventilated during breathing [71].

In the stage of decay, the initial form of the process dominates the X-ray of pulmonary tuberculosis. Thus, the X-ray of the disintegration phase in disseminated tuberculosis is characterized by foci of dissemination and one or more thin-walled, round, as if sealed perifocal non-inflammatory spaces. In the case of focal tuberculosis disease in the stage of decomposition, a small, relatively round and thin ring-shaped shadow is usually detected against the background of limited polymorphic foci, which contains separate foci or is adjacent to its outer contour ("neck" sign is an alternative space). The decay phase of infiltrative tuberculosis is characterized by the presence of the infiltrate and the space in it with a landcart-like closed contour. In the first

stages, such a cavity may contain sequestrations and a small amount of fluid, and its shape is elongated towards the draining bronchus. Then the contours of the cavity are slightly flattened (pneumogenic cavity). When a pulmonary tuberculoma is dissected, a crescent-shaped, sometimes irregular bay-shaped cavity is revealed in its thickness, usually drained by a bronchus located eccentrically at the pole. As the space in the tuberculoma retains this appearance and occupies only a part of it, the process should be defined as tuberculoma in the stage of decay . Only after the wall is completely uniformly thinned can it be considered a cavity formed by a tuberculoma [71].

X-ray of the cavernous form of pulmonary tuberculosis is characterized by the following features:

- limited localization of the process, within one or two segments;
- the absence of typical symptoms of the initial form of the disease;
- well-formed cavity with well-defined external and internal contours of walls of various sizes, often rounded, relatively thin or moderately thick, but with uneven walls and moderate fibrosis around with the presence and presence of several compressed foci.

In rare cases , several hollows are found in the cavern, but they correspond to the above signs. With the development of the cavern, the size of the cavity increases, perifocal infiltration appears around it or bronchogenic spread appears. However, often the development of the cavernous form of tuberculosis leads to the development of fibro-cavernous pulmonary tuberculosis. The X-ray of the fibro-cavernous form of the process is characterized not only by the resulting cavity, but also by the presence of distinct and varying degrees of widespread fibrosis and specific changes in the lungs. The foci are usually polymorphic and mainly of bronchogenic origin [71].

In particular, high-resolution computed tomography has recently become one of the main and promising methods of radiation diagnostics [79].

Due to the pathomorphism of tuberculosis and the variety of clinical, laboratory and X-ray manifestations, the differential diagnosis of the disease is difficult and requires a lot of time for examination. As a result, the time of diagnosis is delayed, which leads to a delay in the treatment of the patient, the appointment of the wrong therapy, the development of the disease, the development of complications, and the deterioration of the patient's quality of life [26, 72, 115].

The most common changes detected during X-ray examination are infiltrative changes in the lungs (X-ray syndrome of limited lung area darkening). According to the literature, infiltrative processes such as community-acquired pneumonia, oncological diseases of the chest organs, exogenous allergic alveolitis and respiratory sarcoidosis, infiltrative pulmonary tuberculosis often lead to errors in the differential diagnosis [49, 77]. Timely and correct diagnosis of infiltrative pulmonary tuberculosis is an urgent task that depends on the possibility of complex application of modern diagnostic methods. According to the literature, the frequency of inconsistency between primary and confirmed diagnoses in the diagnosis of infiltrative pulmonary tuberculosis and community-acquired pneumonia is more than 30%, and the time to diagnosis exceeds 1-3 months [77]. As a result of incorrect diagnosis, approximately 1/3 of

patients with exogenous allergic alveolitis are observed in anti-tuberculosis institutions. [40, 50]. According to 2014 data, the false diagnosis of infiltrative pulmonary tuberculosis in cancer patients was 14%. At the same time, the start of treatment, according to various studies, is delayed from 3 months to 1 year [41]. The use of high-resolution multidimensional computed tomography and radionuclide methods allows to determine in detail the qualitative and quantitative characteristics of infiltrative changes, evaluate functional and static disorders and reach a new level of diagnosis. Etiological and histological examination of the diagnosis plays a special role in the differential diagnosis of infiltrative changes in the lungs, identification of the pathogen, the use of bronchoscopy with a biopsy complex and the use of video-assisted thoracoscopic lung biopsy, extended microbiological research with molecular genetics to reduce the time of diagnostic search. should be transferred, [24, 76]. Errors in the diagnosis of infiltrative pulmonary tuberculosis and community-acquired pneumonia are related to the fact that specific and nonspecific inflammation is an exudative process characterized by the same clinical manifestations of acute inflammation. At the same time, there are also differences in the course of the disease: with pneumonia outside the hospital, they develop quickly, within a few days, changes in the lung parenchyma lead to the formation of intra-alveolar exudation. Tuberculosis disease is characterized by a slow progressive, wave process with relatively rapid formation of caseous necrosis in the focus of inflammation. Thus, for patients with pneumonia outside the hospital, the acute manifestation of the disease, often after hypothermia, is characterized by a large amount of hyperthermia, shivering. The auscultatory picture is also diverse: wet and dry widespread wheezing of different sizes caused by bronchial breathing, bronchospasm. A long prodromal period is more characteristic for infiltrative pulmonary tuberculosis: more than 50% of patients complain of prolonged malaise, reduced work capacity, periodic subfebrile and febrile fever, cough and sweating. Then these complaints disappear from time to time, and again - cough, hyperthermia and other symptoms of intoxication appear, which is often taken as an acute respiratory disease. At the same time, in the last decade, the clinical manifestations observed in patients with these nosological forms are increasingly characterized by the same type and general complaints, which are so specific in each individual case. However, it is unreasonable to make a differential diagnosis based only on the clinical symptoms of the diagnosis. According to most authors, in recent years, the classic clinical presentation is less common, and there are more cases of progressive nonspecific pneumonia with destruction, with less clinical symptoms. According to the literature, specific changes in clinical blood tests in community-acquired pneumonia: leukocytosis (the number of leukocytes usually does not exceed 15-20 thousand), left shift of leukoformula, granular toxic neutrophils, increased ECHT (50-60 mm/h). Also, these patients are characterized by an increase in the index of proteins in the acute phase, in particular, C-reactive proteins, whose values can be 10-20 times higher than normal. At the same time, in acute progressive forms of pneumonia and pulmonary tuberculosis outside the hospital, in particular, in caseous

pneumonia, leukocytosis can reach 20,000 and ECHT can reach 60-70 mm/h. In addition, in some etiological forms of community-acquired pneumonia, despite radiographically widespread changes in the lungs, the patient's hemogram may remain within normal limits [77]. Thus, the analysis of literature data confirms the complexity of diagnosis and differential diagnosis of infiltrative pulmonary tuberculosis and community-acquired pneumonia. From the group of diseases that should be distinguished from infiltrative pulmonary tuberculosis, it is necessary to emphasize the tumor damage of chest organs. According to different authors, the error rate is from 14% to 38.8%, there is an incorrect diagnosis of the oncological process in favor of tuberculosis disease, which leads to long-term, o leads to an average of 45-50 days of follow-up. According to a number of studies, most cases of lung cancer occur in men over 40 years of age [41]. The clinical manifestations of lung cancer are different compared to patients with infiltrative pulmonary tuberculosis, and patients with cancer are characterized by prolonged weakness. Complications in the form of spitting up blood or pulmonary hemorrhage can be observed in both infiltrative tuberculosis and lung cancer. However, in patients with infiltrative pulmonary tuberculosis, as a rule, acid-resistant tuberculosis mycobacteria or mycobacterial DNA are detected in sputum with these complications, which allows for a correct diagnosis [48]. Chest pain can be present in both diseases, the pain syndrome in pulmonary tuberculosis indicates that the pleura is also damaged in the pathological process. These pains are characterized by a pathognomonic syndrome, that is: they are associated with breathing movements and the position of the patient's body. Pain syndrome in oncopathology of respiratory organs is clear, constant, progressive, pain is not related to respiratory movements and occurs in 1/3 of patients [97, 41, 125]. The same diverse appearance can be observed when the tumor is complicated by pneumonic inflammation, compression of vascular trunks, atelectasis or fragmentation of the cancer substrate [67]. In recent years, positron emission tomography has been used to diagnose oncological diseases of the respiratory organs. The principle of its action is based on the high glycolytic activity of tumor formation and, accordingly, the difference in the accumulation of 18F-fluorodeoxyglucose in lung cancer and non-neoplastic diseases [5].

Histological analysis of biopsy material is undoubtedly important in the diagnosis and differential diagnosis of lung tumor diseases. In this regard, bronchoscopy with a biopsy complex plays a major role in the diagnosis and examination of the tumor process. In cases where it is impossible to verify the diagnosis according to the results of fibrobronchoscopy, it is necessary to resort to invasive diagnostic methods - transthoracic lung biopsy or VATS biopsy of the lung or lymph nodes [37, 97].

Currently, the need for differential diagnosis of cases of infiltrative pulmonary tuberculosis and exogenous allergic alveolitis (EAA), characterized by diffuse damage to lung tissue, has increased [49].

In exogenous allergic alveolitis, 3 clinical variants of the disease are distinguished: bronchitic , asthmatic and pneumonic. Difficulties in diagnosis often arise in the pneumonic variant of the

disease. The need for immediate examination of exogenous allergic alveolitis is related not only to incorrect treatment with anti-tuberculosis drugs, but also to direct contraindications to its use. Clinical symptoms of the pneumonic type of exogenous allergic alveolitis are dominated by severe intoxication, signs of respiratory failure, and lung tissue infiltration. As with tuberculosis, the disease proceeds in waves with periods of exacerbation and remission of clinical manifestations. This course of the disease depends on the time of exposure to the allergen and its amount, as well as the interruption of contact with it and the elimination of the antigen from the blood of patients [50]. An early and characteristic sign of exogenous allergic alveolitis is a change in external respiratory function. Hyperreaction of the bronchial tree to specific antigens can be determined during provocation tests. The nature of changes in respiratory function parameters depends on the clinical type of exogenous allergic alveolitis [30].

Radiologically, the differential diagnosis of pneumonia with exogenous allergic alveolitis is difficult, as a rule, it differs little from nonspecific bacterial or viral inflammation in the early stages of the disease, and is often a complication of antibiotic therapy for pneumonia outside the hospital. In this case, as a result of treatment with non-specific antibacterial drugs, the negative dynamics on the X-ray will force you to change the antibiotic, which will further increase the development of changes. X-ray examination shows the interstitial type of infiltration, often one-sided, "frosted glass" symptom of granulomas in the subpleural parts of the lungs and perivascular small foci shadows, increased lung image. In addition, polylymphadenopathy of intrathoracic lymph nodes, reaction of the pleura in the form of exudate accumulation, in advanced cases - pneumofibrosis, stiffness of the diaphragm to the symptom of "cellular lung" [49].

The use of immunological methods for the diagnosis of exogenous allergic alveolitis makes it possible to determine the etiological factor of the disease by determining the free circulating Ig M and Ig G in the patient's blood to suspected allergens, as well as the pathological reactivity of the immunocompetent system [40].

The use of endoscopic examination with the study of bronchoalveolar lavage and biopsy material plays an important role in the diagnosis and differential diagnosis of exogenous allergic alveolitis. The study of the diagnostic material obtained by the bronchoalveolar lavage method allows to assess the condition of the terminal sections of the lungs. In the diagnosis of exogenous allergic alveolitis, the percentage of cellular elements, as well as the components of the inflammatory response, macrophages and leukocytes, are of practical importance [88].

Recently, due to the pathomorphism of the diseases, there are more and more problems in the differential diagnosis of pulmonary tuberculosis and respiratory sarcoidosis, and their incidence rate is steadily increasing [11, 161].

According to the definition of V.P. Molodtsova, sarcoidosis is a polysystemic disease belonging to the group of granulomatosis. The etiology of sarcoidosis remains unknown. The disease mainly affects the lungs and intrathoracic lymph nodes [54]. In the studies conducted under the leadership of AG Khomenko, combined damage of the lung and

intrathoracic lymph nodes is often observed in 65% of cases of respiratory sarcoid. Clinical manifestations of respiratory sarcoidosis are few and non-specific. Often, changes in the lungs are detected accidentally during routine fluorographic examinations. In 27% of cases, sarcoidosis occurs with severe clinical and radiological symptoms: acute onset of the disease, severe intoxication, lymphadenopathy of bilateral intrathoracic lymph nodes, arthralgia, erythema nodosum and acute uveitis, and other symptoms are observed . Along with infiltrative changes, destruction cavities and exudative pleurisy can be observed in 4% of cases [77].

The gold standard for diagnosing pulmonary sarcoid is bronchoscopy with complex biopsy. According to the literature, the diagnostic value of this study is from 30% to 80%. Epithelioid cell granulomas can be detected in 1/3 of patients even in a simple endoscopic picture of the bronchial mucosa, which occurs in almost 20% of cases in pulmonary sarcoid, and in a biopsy. According to the literature, the bronchial tree can be seen as non-specific changes of the banal inflammatory type (endobronchitis, hypervasculature and thickening of the mucous membrane), as well as signs of lymphadenopathy and the presence of tubercles in the epithelium of the bronchi. [63].

Thus, a review of literature data shows that respiratory diseases of very different etiology should be considered as part of the differential diagnosis in the detection of infiltrative changes in the lungs, and complete for etiological or morphological examination. should conduct research [77].

Cavities in the lung tissue occur in various congenital and acquired respiratory diseases: tuberculosis and non-tuberculous infections, neoplasms, vasculitis, etc. [45, 64, 118, 119, 131, 147]. It should be noted that in the progressive stage of tuberculosis, regardless of the initial clinical form of the disease, a cavity of destruction may appear in the lungs. This greatly complicates the differential diagnosis of tuberculosis with other lung diseases manifested by radiological syndrome of cavity formation in the lungs [34, 84, 100]. The complexity of the differential diagnosis of pulmonary tuberculosis is confirmed by the high frequency of discrepancies between the initial and updated diagnoses: in the 50s of the last century in observations - 35-45% of cases [84], in the late 90s - 34-40. % [98], in the 2000s - more than 60.0% [23, 44, 107]. At the same time, both overdiagnosis of tuberculosis and misdiagnosis of diseases of non-tuberculosis etiology have been reported [35, 42, 106]. In recent years, non-tuberculous mycobacteriosis of the lung has been increasingly considered as the cause of the formation of a solitary cavity in the lung [20, 168]. When a cavity in the lungs is detected, the attending physician is tasked with an accelerated examination of the disease, because of the development of severe complications such as the death of lung tissue, bleeding from the lungs, spontaneous pneumothorax the patient's life is in danger [118, 117, 119, 167]. The work of many researchers is devoted to radiation semiotics of pulmonary tuberculosis: Pomeltsova KV (1971), Khomenko AG (1998), Tyurin IE (2003), Ratobylsky GV, Lazareva Ya.V. (2006) and others [75, 80, 98, 99]. In particular, it was noted that the variability of the

destruction space in the lungs and X-ray semiotics largely depend on the initial form of tuberculosis. The size of the cavity in the lungs varies from medium (from 2 to 4 cm), large (4-6 cm) and giant (more than 6 cm) cavities, and the destruction of lung tissue depends on the size, the condition of the surrounding parenchyma and draining bronchi. [98, 99, 101, 106]. Thus, in the stage of destruction of the infiltrative form of tuberculosis, the shape of the destruction cavity in the lungs is often unevenly rounded, the shape of the outer and inner contours depends on the duration of the specific process in the lungs [75, 99]. The most common variant of erosive tuberculoma is eccentric fragmentation near the draining bronchus . In the case of sequestered eroded tuberculoma, there may be difficulties in diagnosis, because this X-ray image is similar to lung abscess or aspergilloma. In such cases, morphological examination is often required to confirm the diagnosis [98, 101]. In the cavernous form of tuberculosis, the cavity is often localized subpleurally, the walls have a rounded shape of the same thickness, there may be perifocal foci of inflammation in the surrounding lung tissue and a "path" to the lung root [75, 99].

Features of the clinical course

Tuberculosis is an infectious disease, and the most important areas of its fight are the detection of new cases and their clinical treatment [56, 113, 114]. First of all, the risk of the spread of infection is caused by patients with tuberculosis, which leads to the expansion of the territorial boundaries of the epidemiologically dangerous foci of tuberculosis infection, depending on the presence of bacterial excretion, destruction of lung tissue, and the presence of additional risk factors. [10]. Hospital-substitute technologies are unacceptable for such patients, who must stay in the hospital around the clock until ablation [103]. At the same time, the effectiveness of the treatment of newly diagnosed patients is low , according to the results of one year of therapy, it is necessary to close the cavity of newly diagnosed patients - 61.7%, to stop the release of bacteria - 69.8%, clinical recovery can be achieved - 35.7%. [13, 61, 81, 94]. It follows that in every third patient tuberculosis can turn into a chronic form. Therefore, much attention is paid to the analysis of clinical and X-ray examination data of the patient for diagnostic purposes. The clinical presentation of the disease during the period of destruction of lung tissue and the appearance of a cavity in the lungs, characteristic symptom complexes: dry cough or sputum of different volume and quality (purulent , mucous, bloody), chest pain, subfebrile body temperature, loss of appetite, weight loss, reduced physical capacity, anemia, leukocytosis, increased ECHT are observed [118, 117, 119, 167]. The clinical manifestations of tumors and infectious processes in the lungs can be different or have many common symptoms. For example, the acute onset of the disease is sometimes a poor-quality tumor helps to distinguish from an infectious process, but with an infection, as in an oncological process in the lungs, hemoptoe can occur. [111]. A characteristic symptom of abscess drainage into the bronchial tree is a large amount of muco-purulent, purulent or bloody purulent sputum when coughed up as a "full mouth" [107, 111].

Cavernous tuberculosis is distinguished from other clinical forms of

pulmonary tuberculosis by the formation of an isolated and stable size cavity without obvious infiltrative and fibrotic changes in the lung tissue. It occurs in 5-10% of cases.[48].

Cavernous pulmonary tuberculosis can be accompanied by the presence of an air cavity without obvious inflammatory and fibrotic changes in its wall and pericavitary lung tissue, as well as asymptomatic or mild signs of intoxication and chest complaints. This is due to the formation of cavernous tuberculosis in the background from other clinical forms after long-term chemotherapy. A tympanic sound is heard on percussion in the lung branch where the cavity is located, on auscultation, wet and dry wheezing is sometimes heard against the background of weakened vesicular breath, in most cases the cavities are "mute", i.e. cannot be determined by physical means. Fibrosis - cavernous pulmonary tuberculosis is a chronic cavernous process, characterized by the presence of several or one cavity, in the wall of which there is a lot of thick fibrous tissue in the surrounding lung tissue. Among newly diagnosed patients, patients with fibrosis - cavernous and cavernous pulmonary tuberculosis make up 5 - 6%, among patients observed in the dispensary for active tuberculosis - 8 - 10%.

The following clinical forms are distinguished with fibrous-cavernous pulmonary tuberculosis:

- stable fibro-cavernous pulmonary tuberculosis;
- progressive fibro-cavernous pulmonary tuberculosis;
- with progressive complications;

Fibrosis - complications of cavernous pulmonary tuberculosis occur in 75 - 80% (lungs - heart failure, spitting blood, bleeding, amyloidosis of internal organs, spontaneous pneumothorax). Symptoms of intoxication and chest complaints are expressed in patients with fibrosing-cavernous pulmonary tuberculosis . In the common severe progressive form complicated by caseous pneumonia, patients suffer from severe sweating, high fever, shortness of breath, coughing up sputum up to 50-100 ml per day, sometimes mixed with blood. Auscultation reveals bronchial breath in the affected area, amphoric breath in large spaces, wet rales with small and medium bubbles depending on the size of the draining bronchi. During remission, patients may develop nonspecific bronchitis, shortness of breath due to bronchiectasis, cough with sputum, and pneumosclerosis. Remission in fibrosing-cavernous pulmonary tuberculosis is an unstable condition, and if not treated, the process may worsen with symptoms of intoxication and chronic inflammation characteristic of this form [48].

Treatment of destructive pulmonary tuberculosis

Fibrosis-cavernous pulmonary tuberculosis is one of the most severe forms of the disease, taking the leading place with tuberculosis infection and a mortality rate of at least 40% [19, 46, 66]. According to XK Aminev, (2011) out of 643 patients, clinical treatment of fibro-cavernous pulmonary tuberculosis was achieved in only 101 (15.7%) patients. 204 (31.7%) patients died, of which 131 (20.4%) patients died before 1 year. 173 (26.9%) patients died of other causes [3].

Analysis of the causes of death of patients with tuberculosis in St. Petersburg in 2016. Balasanyants GV and others. (2016) found that the clinical form of

patients who died in 45.1% of cases was also fibro-cavernous tuberculosis disease [6].

In the formation of fibrous-cavernous tuberculosis, the effectiveness of conservative treatment ranges from 0.5 to 8%, the cessation of bacterial excretion is observed in at least 40% of patients [18, 51, 177, 179].

Mishin V.Yu. (2009) published their experience of conservative treatment of 41 patients with pulmonary tuberculosis. The dominant form of the disease was fibro-cavernous tuberculosis (73.1%). After 3 months of chemotherapy, the sputum of 10 (24.4%) patients had a negative result, and after 6 months of treatment, 28 (68.3%) patients achieved cessation of mycobacterial shedding. Closure of decay cavities occurred only in 6 (14.6%) patients [53].

Many Russian and foreign researchers recognize chronic destructive forms of tuberculosis and multidrug resistance of mycobacteria as a direct indication for surgical treatment [8, 22, 126, 130, 148, 165, 173, 181].

The time of surgery, the spread of the process, the presence of MDR/XDR tuberculosis disease, the severity of the accompanying pathology, etc. have a significant impact on the effectiveness of surgical treatment of fibro-cavernous tuberculosis. [8, 22].

To date, the optimal duration of operations in patients with fibrous-cavernous tuberculosis has not been clearly defined. Many authors consider the existence of a long-term gap without a healing tendency to be a direct indication for surgery, especially in the presence of drug resistance [83, 90, 138, 170].

Subotic D. and others. (2016) recommend surgical treatment no later than 6-8 months after initiation of anti-tuberculosis treatment [171]. Excessive delay in surgery may contribute to disease progression and increase the spectrum of drug resistance [155]. Vorochikhin TA and others. (2018) reported the best results of surgical treatment in patients who underwent surgery before 2 years of conservative treatment [18].

Surgical methods have been and will remain an important step in the complex treatment of patients with respiratory tuberculosis, and especially patients with fibro-cavernous pulmonary tuberculosis. A significant reduction in the number of patients with fibrous-cavernous tuberculosis can be achieved only with the joint cooperation of a phthisiatrician and a thoracic surgeon [8, 82, 124, 128].

Specificity of the blood coagulation system and inflammatory processes in tuberculosis

The role of various inflammatory cells, cytokines, and immune effectors mediating the development of granulomatous lesions in tuberculosis is noteworthy. In response to this infection, immune cells produce some pro-inflammatory cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-α, which affect homeostasis [145]. These changes include an increase in procoagulant activity, prothrombin time (PT), fibrinogen and D-dimer, activated partial thromboplastin time (aPTT), a decrease in anticoagulant factors (antithrombin III, protein C, protein C) and attenuation of fibrinolysis leading to a hypercoagulable state [133, 174].

Tuberculosis infection is characterized immunologically by acute phase responses and hematologically by activation of procoagulation, reduction of

anticoagulant and disruption of fibrinolytic system [120, 149]. This disease can lead to thrombosis through various mechanisms, including the production of pro-inflammatory cytokines, venous damping, and local invasion. Prothrombin time, fibrinogen level, aPTT, and D-dimer levels were higher in advanced lesion and BK positive sputum group. In a cohort study, pretreatment BK-positive patients had higher levels of IL-6 and interferon-γ (=0.035) than BK-negative patients [123]. Immune complexes developed in various infectious diseases and many other factors stimulate the production of IL-1, IL-6, TNF-α, which increases the stimulation of endothelial cells, monocytes and macrophages, and stimulates internal and external pathways. initiates coagulation activity through [175, 134] Increases in fibrin breakdown products (FDP) or D-dimers are nonspecific indicators that fibrinolysis has occurred. Fibrin degradation products measure only breakdown products, whereas D-dimers are more specific indicators and measure thrombin and plasmin activity by detecting newly formed and newly degraded fibrin (15–17). D-dimers enhance inflammatory mediators such as IL-1, IL-6, and their levels also increase during atherosclerosis. [169]. A significant decrease in PT, aPTT, fibrinogen and D-dimer levels was observed after intensive phase treatment [172] The goal of intensive treatment is to eliminate mycobacteria and improve symptoms. With the reduction of mycobacteria, blood clotting factors are affected, they return to normal levels in the plasma. This may be responsible for the prolonged PT and resolution of APTT as therapy continues. The reduction of fibrinogen occurs because the acute phase reaction of the liver is reduced even after treatment with anti-tuberculosis drugs, so fibrinogen is no longer produced in large quantities, which leads to a decrease in its concentration. Thus, fibrinogen may also be a useful marker for monitoring therapeutic response in the treatment of tuberculosis [121]. With anti-tuberculosis therapy, regeneration of the endothelium damaged by tuberculosis infection occurs. This leads to a decrease in the production of plasminogen activator inhibitor, as well as inactivation of thrombin-activated fibrinolysis inhibitor. These inhibitors suppress excess (secondary) fibrinolytic activity, as a result of which normal (primary) fibrinolysis is restored with a decrease in the accumulation of fibrin breakdown products and D-dimer [122]. In conclusion, pulmonary tuberculosis infection is associated with hypercoagulability, which is characterized by increased hemostatic parameters, which significantly improves after intensive phase treatment [172].

The search for new laboratory signs of the infectious process in tuberculosis, which indicates the severity of the disease and serves as a criterion for the effectiveness of therapy. Any inflammatory process, including tuberculosis, various proteins of non-specific immunity, proteins of the acute phase of inflammation and trigger non-specific and specific immune responses It is accompanied by the production of inflammatory cytokines, the detection of which can indicate the presence of inflammation and its complexity. Currently, one of such non-specific markers characterizing the severity of the general infectious process is procalcitonin, a calcitonin prohormone discovered in 1984 [151]. In patients with active tuberculosis, the level of PCT is higher

than in healthy people, but its concentration is much lower than in patients with sepsis and septic shock [176]. In addition to thyroid gland cells, under the influence of lipopolysaccharides (LPS), procalcitonins are synthesized in neuroendocrine cells of the lungs, liver and, to a lesser extent, kidneys and blood monocytes. It was shown that the procalcitonin molecule has two invaginations in its spatial structure capable of binding and inactivating LPS activity from different sources. Experimentally and clinically, procalcitonin production has been shown to be stimulated by various pro-inflammatory cytokines, such as interleukin (IL)-6, IL-8, and tumor necrosis factor-α (TNF-α) [123].

Conclusion: Thus, scientific works devoted to the problem of evaluation of changes in procalcitonin and blood coagulation system in the course of the destructive form of tuberculosis of the lungs are rare in the world literature. The problem is urgent and requires further research with the search for new diagnostic approaches and improvement of modern methods of treatment.

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