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# COMPARATIVE AETIO-EPIDEMIOLOGICAL ANALYSIS OF LUNG TUBERCULOSIS VERSUS SARCOIDOSIS: CLASSICAL AND NEW CONCEPTS

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The review presents data on two similar granulomatous inflammatory diseases: tuberculosis and sarcoidosis of the lungs, which together cover about 5% of all pulmonary pathology, albeit occur with different incidence (20 : 1). Despite the established aetiology of tuberculosis, the disease has not disappeared and nowadays has even acquired a new urgency: It is getting out of control due to growing poverty, the comorbidity with HIV infection, increasing cases of drug resistance of Mycobacteria, insufficient effectiveness and the growing costs of its treatment. Against the background of the expansion of anthropogenic influences and other environmental impacts on the immune system, the incidence of lung sarcoidosis is also increasing, while patients are initially often misdiagnosed with tuberculosis, with resulting unjustified anti-tuberculosis chemotherapy, leading to chronization of the disease with frequent relapses and, accordingly, to an increase in disability and mortality rates. In recent years, clinical manifestations of sarcoidosis due to a variety of trigger aetiological factors with adjuvant-like action (from Mycobacteria to xenobiotics) – are considered by a number of authors as a variant of autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA). The article emphasizes the similarity of two granulomatous inflammatory diseases and the concept of two variants of the body's response to similar or even identical aetiological factors within different human reactivity (possibly on a different mosaic/permissive background). In brief the newest data on experimental models of sarcoidosis are reviewed as well as the role of autophagy disorders and opposite macrophageal polarization in tuberculosis versus sarcoidosis. Authors coined the original hypothesis of the possible therapeutic effectiveness of Rapamycin in sarcoidosis and for the first time posed a question of equivocal character of comorbidity between these granulomatoses and COVID-19 infection.

**Keywords:** adjuvant, ASIA-syndrome, autoimmunity, granulomatosis, polarization of macrophages, Rapamycin, sarcoidosis, tuberculosis, epidemiology, etiology.

# СРАВНИТЕЛЬНАЯ ЭТИО-ЭПИДЕМИОЛОГИЧЕСКАЯ ХАРАКТЕРИСТИКА ТУБЕРКУЛЕЗА И САРКОИДОЗА ЛЕГКИХ: КЛАССИЧЕСКИЕ И НОВЫЕ ПРЕДСТАВЛЕНИЯ

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В статье приведены данные литературы, посвященные сходным гранулематозным воспалительным заболеваниям — туберкулезу и саркоидозу легких, которые составляют вместе около 5 % всей легочной патологии, но встречаются с разной частотой (20 : 1). Несмотря на установленную этиологию туберкулеза, болезнь не исчезла и даже приобрела новую актуальность: заболевание выходит из-под контроля из-за растущей бедности, связи с ВИЧ-инфекцией, учащения случаев лекарственной устойчивости микобактерий, недостаточной эффективности и растущей стоимости лечения. На фоне расширения антропогенных влияний и других экологических воздействий на иммунную систему растет и заболеваемость саркоидозом легких, при этом пациентам первоначально зачастую ставится ошибочный диагноз туберкулеза, с необоснованной противотуберкулезной химиотерапией, что ведет к хронизации патологии с частыми рецидивами и, соответственно, — к возрастанию инвалидизации и летальности. В последние годы клинические проявления саркоидоза из-за разнообразия триггерных этиологических факторов адъювантоподобного действия (от микобактерий до ксенобиотиков), рассматриваются рядом авторов как вариант аутоиммунно/аутовоспалительного синдрома, вызванного адъювантами (ASIA — Autoimmune/Inflammatory Syndrome Induced by Adjuvants). В статье подчеркивается сходство двух гранулематозных воспалительных заболеваний и возможность их трактовки как двух вариантов ответа организма на близкие или даже тождественные этиологические факторы при различной реактивности (возможно, на разном мозаично-пермиссивном фоне). Кратко охарактеризованы новые модели саркоидоза и роль нарушений аутофагии и направления поляризации макрофагов при туберкулезе и саркоидозе. Высказана оригинальная авторская гипотеза о возможной эффективности рапамицина в лечении саркоидоза, впервые ставится вопрос о неоднозначных коморбидных взаимоотношениях данных гранулематозов и новой коронавирусной инфекции.

**Ключевые слова:** адъювант; аутоиммунно-аутовоспалительный синдром, индуцированный адъювантами; аутоиммунитет; аутофагия; гранулематоз; поляризация макрофагов; рапамицин; саркоидоз; туберкулез; этиология.

Pulmonary tuberculosis (PT) and sarcoidosis (PS) refer to diffuse productive granulomatous inflammatory diseases and together account for about 5% of all pulmonary pathology, occurring in a ratio of about 20:1 [78]. According to the literature, 50–70% of patients with PS are initially misdiagnosed as PT with unjustified antituberculosis chemotherapy, which leads to the chronicity of the process with frequent relapses and, accordingly, to an increased risk of disability and mortality [9, 21].

## EPIDEMIOLOGY AND ETIOLOGY OF TUBERCULOSIS

In the last quarter of the last century, some experts considered tuberculosis to be a "vanishing disease," but this turned out to be a deep and global mistake that the World Health Organization (WHO) even declared the "rebirth" of this disease to be an extraordinary event in the world in 1993. According to WHO reports, in 2018, more than 10 million people fell ill with tuberculosis, including 5.7 million (57.0%) men, 3.2 million (32.0%) women, and 1.1 million (11.0%) children. In addition, two-thirds of new cases (67.0%) were found in eight countries (in descending order of the number of cases): India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa. Moreover, more than 484,000 new cases have become infected with multidrug-resistant (MDR) *Mycobacterium tuberculosis* (MBT). In 2018, more than 1.5 million people died from tuberculosis worldwide (including 0.25 million with concomitant human immunodeficiency virus (HIV) infection); therefore, tuberculosis infection remains one of the 10 leading causes of death globally, ahead of other diseases that attract much more scientific and public attention including HIV infection, malaria, and the new coronavirus (COVID-19) infection [12, 89]. According to the generalized Chinese experience, PT does not make patients more susceptible to COVID-19 infection; but when comorbid, its risk for its severe course increases by more than two times [61].

PT is an infectious disease, and its causative agent, MBT, was discovered by the founder of monocausalism in pathology, Robert Koch (1843–1910), back in 1882. Today, it is known that the disease can in principle be caused by *M. tuberculosis*, *Mycobacterium bovis*, and *Mycobacterium africanum* and has been proven by experimental work; its main route of infection transmission (responsible for more than 95% of cases) is airborne. But over a century and a half, it became clear that many conditions, particularly the main internal condition, that is, the reactivity of the body, significantly affect the onset, development, and course of the disease [54].

Koch himself called PT "tears of poverty" since the incidence of the population directly depends on its standard of living. In economically developed countries, including the USSR, the stabilization of the main epidemiological indicators was noted at a very low level in the second half of the last century, supporting the optimism of specialists regarding the process of eliminating tuberculosis as a mass disease [19]. But in both Russia and other

former USSR republics, after many years of stabilization, the incidence of PT increased significantly due to the disintegration of the country and the socioeconomic crisis in the 1990s. Although the indicators slightly improved from 2008 to 2017 in the Russian Federation, the overall incidence regressed from 85.1 to 48.3 per 100,000 population (43.2%), and the incidence in children aged 0–14 years decreased from 15.3 to 9.7 per 100,000 (36.6%) [30].

Men more often suffer from PT (69–75%), but there have been recent reports of several cases of the disease among children, adolescents, and pregnant women [24, 89]. We must not forget that overdiagnosis of tuberculosis is possible due to an increase in the number of cases of mycobacteriosis caused by nontuberculosis mycobacteria [34].

After isolating a group of proteins that are expressed during MBT reproduction (ESAT-6 and CFP-10), new immunological diagnostic tests *in vitro* (interferon gamma release assay [IGRA] tests: QuantiFERON-TB, T-SPOT.TB, and IP-10) and *in vivo* (recombinant tuberculosis allergen and Diaskintest) were performed [15]. Diaskintest is a national protocol, and it uses ESAT-6 and CFP-10 proteins, which are absent in *M. bovis* from the Bacillus Calmette–Guérin vaccine, as allergens, which make it possible to distinguish post-vaccination allergy from infectious ones [12, 18]. However, it turned out that using the above tests could not reliably perform differential diagnostics between latent tuberculosis infection (LTI) and active tuberculosis (AT), since equally positive results are noted in these variants of the process. In the presence of characteristic X-ray changes, bacteriological verification of the diagnosis of AT was obtained only in 46% of cases, and the determination of specific immune complexes (ICs) by dynamic light scattering after the addition of *in vitro* antigens of specific peptides ESAT-6 and CFP-10 made it possible to determine AT in 100% of cases and identify a high-risk group of patients with LTI [25]. In 2014, the WHO defined LTI as the state of constant immune response to MBT without AT and recommended interpreting IGRA and similar tests [26].

All these data indicate that mycobacterial causative factors alone do not exhaust the entire etiology of tuberculosis. The course of tuberculosis depends on the body's response to MBT, which, to the extent of the reactivity of individuals, primarily immunological one, can vary [55].

Currently, in both individual regions of our country and the Russian Federation as a whole, there is a formation of a severe clinical structure in the form of destructive and bacillary tuberculosis, its combination with HIV infection, and the formation of MDR forms of MBT [28]. Effective treatment in such patients is noted only in 26% of cases, and complications of chemotherapy (toxic damage to the hearing organs, liver, and kidneys) often force doctors and patients to refuse to continue treatment [17]. 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 treating with drug-sensitive MBT [14].

With incurable PT and many concomitant diseases (liver and kidneys) leading to mortality, "palliative care" programs are being developed for patients [3, 12, 52].

WHO experts call for another "elimination" of PT by 2030, but it is difficult to imagine since the incidence of PT in the population depends on many conditions as follows: (i) genetics and regions (demographic, social, economic, living standards, education, and migration intensity and direction); (ii) politics and economics (crises and conflicts); (iii) the prevalence of tuberculosis in the penitentiary system; (iv) the effectiveness of antituberculosis measures of institutions of general medical and specialized networks (prevention organization, timely detection, laboratory and X-ray service quality, and effective treatment) [12, 13, 42]. In view of this, there are also pessimistic forecasts: tuberculosis has got out of control in Africa because of the growing poverty and extremely widespread HIV infection, and MDR MBT threatens to destabilize efforts to combat the infection in many socially and economically prosperous regions. The problem of PT, despite the established etiology of the disease, has not disappeared and even acquired new urgency [55].

## CLINICAL AND PATHOPHYSIOLOGICAL FEATURES OF SARCOIDOSIS

Sarcoidosis is a polysystemic disease of unknown etiology with a heterogeneous clinical course, characterized, as a rule, by the formation of noncaseating epithelioid cell granulomas and accumulation of $CD4^+$ T-lymphocytes in the foci of productive inflammation in Th1/Th17-dependent immune responses. According to modern data, sarcoidosis is characterized by a predominance of polarization of macrophages toward the M2 phenotype, whereas in tuberculosis, the M1 pathway predominates [11, 53].

The pathomorphological substrate of the disease is the result of delayed-type hypersensitivity – epithelioid cell granuloma (a compact accumulation of mononuclear phagocytes), macrophages,

and epithelioid cells with the presence of giant multinucleated cells, lymphocytes, and granulocytes (or without the latter). The processes of transformation, recruitment, and final differentiation of cells in granulomas are controlled by cytokines and chemokines, which are communication peptides of the immune system [32, 33].

Recently, there has been a noticeable increase in the incidence of PS, which is associated with both an improvement in diagnosis and a true increase in the incidence of this form of pathology, which in all countries where antituberculosis vaccination was introduced had a reciprocal dynamics with respect to tuberculosis infection [1]. Women suffer from sarcoidosis more often. According to US data for 17 years, there has been a slight increase in mortality from sarcoidosis in both women and, to the greatest extent, men, especially among African-Americans [67].

As a rule, the contingent of patients with PS is those aged 20–50 years, who, with rational management, have a good prognosis for restoring health and working capacity. However, sarcoidosis can also affect preschool children, adolescents, and the elderly [24, 81].

The geoepidemiological picture of sarcoidosis is characterized by several features. Its prevalence among African-Americans is 2–7 times higher than among US citizens of other ethnic origins and is more than 100 cases per 100,000, and in Scandinavian countries, it is 40–70 cases. Meanwhile, in Korea, China, tropical African countries, Australia, and the Southern Hemisphere in general, it is less frequent than in the Northern Hemisphere countries, which are associated with not only regional natural features but also the absence or low intensity of disease detection programs [41, 67, 70].

In Russia, the incidence of PS until 2003 was analyzed only according to the statistics of antituberculosis dispensaries and ranged from 2 to 7 per 100,000 adult population [29]. In Kazan, the first active screening of these patients was performed in 2002, and the prevalence was 64.4 per 100,000. Cases of familial sarcoidosis occurred in 3%, whereas this indicator was 1.7% in the UK, 9.6% in Ireland, 3.6% in Finland, and 4.3% in Japan. According to recent studies, the prevalence of PS in Russia has regional variations from 22 to 47 per 100,000 population [33]. In Karelia, the recorded prevalence is 73 per 100,000 [6]. Women with PS have more pronounced clinical manifestations of the disease than men, which is characteristic of many diseases of autoimmune origin [73]. In this case, the mortality rate ranged from 0.3% to 7.4%, and the consequences of cardiac, respiratory, and renal failure and severe concomitant oncopathology are common causes of death [6, 60]. The death of patients is also possible from the addition of (or activation of latent) nonspecific and PT infection, HIV infection, and leprosy – primarily due to immunosuppressive therapy used in sarcoidosis [8, 83].

The mortality rate of PS in the British reference group was 10 times higher (4.8%) than in the general population (0.5%) because of the side effects of using immunosuppressive drugs [56].

The etiology of PS remains unclear, although it was recently associated with the difficulty of creating adequate experimental models; however, there are several nonmutually exclusive hypotheses.

The hypothesis of its infectious etiology is confirmed experimentally by the possibility of PS transmission during transplantation of donor organs to humans [76]. Infectious factors are considered 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 [46]. According to molecular microbiological, epidemiological, and immunological studies, the triggers of PS most often include mycobacteria (classical and filterable forms) and *Propionibacterium acnes*. When immunized with the latter, along with Freund's adjuvant, pathogenic mice produced granulomatosis similar to PS [77]. In the 1960s, in the USSR, MBT with cell wall defects were often isolated from granulomas and bronchial lavage and from the blood of patients with skin and eye sarcoidosis and PS [6]. However, in countries with low MBT infection rates (New Zealand), high rates of isolation of MBT in sarcoidosis, recorded where LTI and tuberculosis are common, have not been confirmed [7, 9].

Less often, in sarcoidosis, data are described in favor of the etiological role of other pathogens such as *Chlamydophila pneumoniae*, *Borrelia burgdorferi*, molds, fungi, and certain viruses including hepatitis C, herpes group, and JC-polyomavirus type 2. There have been reports of a positive effect of some antibiotics in sarcoidosis [43, 45, 87].

However, the latter cannot be considered unequivocal evidence in favor of the infectious etiology of the disease. After all, many antibiotics interfere with various metabolic and signaling processes in the cells of the body itself. In this regard, it seems important to us to emphasize the following circumstances.

Recent advances in modeling sarcoidosis provide another way of understanding it, interpreting this disease not as purely infectious but as autoinflammatory [80].

It appears that sarcoidosis may be critically dependent on the disruption of macrophage polarization along the M1/M2 pathways. Macrophages of the M2 phenotype, usually involved in multinucleated cell formation, are overexpressed in sarcoid granulomatosis in all involved tissues. The recently proposed model [53] explains well the early events of granuloma formation in various granulomatoses with a pronounced shift in the polarization of macrophages along the M2 pathway in sarcoidosis but not in tuberculosis. The polarization of macrophages into M2 cells depends on a key mechanism: the rapamycin-sensitive mTOR signaling pathway [63].

This pathway inhibits autophagy in macrophages, preventing the elimination of the agents that caused chronic granulomatous inflammation [77].

In our opinion, chronic signaling through the mTORC1 kinase is the most successful experimental model of sarcoidosis to date, and the main element of this pathway marks sarcoid granuloma formation and sarcoidosis progression. Knockout mice with impaired mTOR regulation and autophagy have been obtained, in which sarcoidosis-like systemic granulomatosis develops spontaneously [72]. In this regard, we hypothesize that an off-label antibiotic from the transplant arsenal, rapamycin, may serve as an effective drug against sarcoidosis. Although our hypothesis has been published [84], it has never been clinically tested and needs such verification. A literature analysis reported at least one case of sarcoidosis registered *de novo* in an Italian patient with liver transplantation, which regressed after using rapamune (an analog of rapamycin) for transplant indications; however, cyclosporin therapy did not prevent it [75]. This case indirectly confirms both the impossibility of interpreting the therapeutic effects of antibiotics as an unequivocal proof of the role of infections in the etiology of the process and the validity of our proposed medical community to test the idea of treating sarcoidosis with rapamycin.

The hypothesis of the influence of "environmental factors" [40] proceeds from the fact that antigenic, haptenic, and/or adjuvant properties and the ability to stimulate the formation of similar to tuberculous granulomas are possessed not only by microbial pathogens but many inanimate agents – smoke and chalk particles, silicon and carbon-containing nanoparticles and nanotubes, printer and copier toners, implanted prosthesis silicone, tattoo pigments, asbestos, some dyes, agricultural, and road and metal dusts containing aluminum, barium, beryllium, cobalt, copper, mercury, gold, lanthanides, titanium, and zirconium [62]. For many of such agents, this has been confirmed in experimental models. In epidemiological studies of a case-control etiology study of sarcoidosis, professionals and other scientists have also shown an increased risk of occupational PS in workers associated with exposure to these ingredients [39, 77, 86]. There is a hypothesis postulating that disorders or blockades of autophagy in macrophages that have invaded foreign bodies or pathogens promote the persistence of these agents inside the macrophage and formation of granulomas including sarcoidosis [77].

Hypotheses about the role of exogenous anthropogenic and/or natural factors in the etiology of sarcoidosis and the role of impaired autophagy and polarization of macrophages in its development do not contradict the ideas about its autoimmune and/or autoinflammatory pathogenesis that have been actively developing in recent years [26, 40, 85].

According to official sources, more than 4 million toxic substances have been registered in the world today, and their number is increasing by at least 6000 every year [16]. These substances can have a direct toxic effect on cells, and when they die, they produce autacoids that trigger inflammation mechanisms, and, in accordance with the "danger hypothesis," through increased expression of costimulatory molecules on immunocompetent cells and prolongation of the existence of immunosynapses, they have the ability to expand the autoimmunity spectrum and increase autoantibody titers [32].

When cells are altered by toxicants, neoantigens can be formed to which the individual's lymphocytes are not tolerated, which stimulates immunopathological processes. Meanwhile, 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 reaction-active attacking cell membranes and compound biopolymers, mainly epoxy and epoxide nature, with free radical properties. Many of them, having trigger and adjuvant effects, activate the mediator systems of inflammation and cause allergic reactions [51].

Therefore, an increase in the chemical load exerted on individuals by xenobiotics entering the body is associated with an increase in immunopathological diseases, and allergies, including drug

allergies, occur in at least 20% of the population. It is characteristic that immunostimulating and adjuvant drugs, in particular as new means of cancer therapy (inhibitors of T-lymphocyte checkpoints and interferons and aluminum compounds used for about 100 years in vaccinology and dermatocosmetology), could provoke sarcoidosis in some individuals [49]. According to Judson, the number of sarcoidosis cases associated with drug and other iatrogenic effects on immunoreactivity is growing epidemically in the current century [66]. Endogenous intoxication, that is, excessive systemic action of autacoid biologically active substances, largely determines the severity of organ dysfunctions of natural detoxification, in particular the liver, kidneys, and lungs, which significantly affects the consequences of exogenous intoxication [10, 32, 61]. It is characteristic that the incidence of some autoimmune diseases in different regions of the Russian Federation has been growing over the past several years and differs regionally by tens of times, correlating with urban environmental factors, particularly the automobile and road complex [23]. According to Zinchenko et al. [90], the trigger anamnestic factors that were statistically significantly correlated with both the presence of clinical signs of autoimmune/autoinflammatory syndrome in PS and their severity include occupational hazards (especially constant contact with printers), severe prolonged stress, and more than three pregnancies in anamnesis. There is evidence that, in general, PS occurs less frequently among smokers than nonsmokers, but at the same time, the dysfunctions and interstitial changes in the lungs in sarcoidosis of smokers are more pronounced, and the diagnosis is made late since PS passes "under the guise" of other diseases [2]. In smokers, pulmonary macrophages and nicotine immunomodulatory effect prevent T-lymphocytic infiltration in the lungs, and therefore, extrapulmonary manifestations of sarcoidosis are more often observed [40].

The frequency of family diseases of PS in individual countries was indicated, and the most probable hereditary factors include genetic features of the regulation of the immune response that increase the risk of developing several classic autoimmune diseases: variants of the human major histocompatibility complex (HLA) haplotype, tumor necrosis factor-alpha gene polymorphisms, angiotensin-converting enzyme (ACE), vitamin D receptors, T-lymphocytes inhibitory receptors, mTOR pathway participants of intracellular signaling, and proteins that regulate the autophagy process [40, 57, 76, 77, 85]. Thus, in early acquired sarcoidosis in adolescent and pediatric practice, as well as in the similar monogenic hereditary Blau syndrome, a common genetic defect in the *NOD2* gene, the most important regulator of innate immunity expressed in antigen-presenting cells and also involved in autophagy processes, was found [44, 77].

One of the tendencies of the last decade in the doctrine of sarcoidosis is to bring it closer to the autoimmune/autoinflammatory syndrome caused by adjuvants – autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA), first described by Schoenfeld and Agmon-Levin in 2011 [82]. This syndrome initially included five autoimmune or suspected autoimmune disorders, namely, post-vaccination syndrome, siliconosis, macrophage myofascial syndrome, Gulf War syndrome, and unhealthy building syndrome. In all ASIA cases, the development of autoimmune inflammation is preceded by contact of people with trigger factors – adjuvants in the presence of an individual genetic predisposition. At the same time, the mechanisms of autoimmunity induction can be different; pathomorphological signs of immune inflammation are present in the tissues, including lymphohistiocytic infiltration, granulomatous inflammation, and scleroderma-like changes. A characteristic feature is the regression of clinical, laboratory, and pathological manifestations that occurs after the termination of contact with the adjuvant [20, 82]. The evidence for a link between sarcoidosis and ASIA is growing. In particular, a study of the international registry of patients with ASIA found 8 cases of sarcoidosis per 500 cases, which is statistically significantly associated with the use of silicone implants [88]. Studies in the Netherlands have confirmed the link between sarcoidosis and chronic exposure to silicone prostheses, especially in individuals with allergic immunoreactivity [50]. Many works emphasized that sarcoidosis is often combined with other autoimmune diseases (Hashimoto's thyroiditis, Sjogren's syndrome, rheumatological diseases, and immunopathological vasculitis) and is associated with certain features of the main histocompatibility complex haplotype (the presence of HLA-DRB1*0301 and HLA DQB1*0201).

In sarcoidosis, some autoantibodies have been registered (vimentin and its citrullinated derivatives and peptides from the composition of lysyl-tRNA synthetase, ATP synthase, zinc finger protein 688, and mitochondrial ribosome protein L43), and there are cross-immune reactions of autoantigens with autoantigens (heat shock proteins of mycobacteria Mtb-HSP70, Mtb-HSP65, and Mtb-HSP16, mycobacterial protein katG, and antigens of propionic

acid bacteria of acne). Sarcoidosis, like several classic autoimmunopathies, is associated with lymphocytic infiltration of the affected organs, with a predominance of Th1/Th17 lymphocytes, and it is reduced by immunosuppressant. The disease is characterized by peculiarities of subpopulation spectra of lymphocytes in the blood typical for autoimmunopathies [11, 25, 40, 69, 90]. All these are indirect arguments in favor of the autoimmune/autoinflammatory nature of sarcoidosis. The direct criteria of the autoimmune nature of SL, in accordance with the classical postulates of Vitebskiy and Rose, could include its models based on the action of the corresponding autoantibodies, including during the transplacental passive transfer from the mother or immunization with autoantigens [32, 85], but there is no such information yet. However, a model of sarcoidosis-like noncaseating granulomatosis in Tsc2 –/–knockout mice with impaired autophagy and macrophage polarization exists, and rapamycin inhibits the process in such animals [72], which also indicates the justification of the proposed use of this drug in PS therapy.

## PS AND PT: DIFFERENT ANSWERS TO ONE ETIOLOGICAL FACTOR?

According to Refs. [25, 85, 90], no ICs were detected in the blood serum of patients with PS after exposure to antigens of the recombinant tuberculosis allergen (ESAT-6/CFP-10), but the latter was detected after exposure to antigens of the "extract of lung tissue." This does not speak in favor of the etiological role of MBT and indicates an autoimmune reaction to its own lung tissue in PS. It is easy to link these data with the classical use of the Kveim allergy test as evidence of sarcoidosis because the Kveim reagent was extractable autoantigens of the patient's lymphoid organs and showed a positive skin test in sarcoidosis, in contrast to tuberculin, and vimentin was found in the composition of this reagent by proteomic analysis [58, 71]. However, vimentin is a modifiable participant in any, including tuberculous, granulomatous processes, which is why a recent comparative analysis of two granulomatosis revealed autoantibodies to this protein and its modifications, in both this case and other granulomatous lung diseases, in contrast to nonspecific pulmonary pathology [25, 26, 84].

Furthermore, according to modern data, PT is also a disease that is not free from a pathogenetically significant autoimmune component [59]; therefore, the differential diagnosis between PT and PS can hardly be based on autoreactivity to a particular antigen alone [48].

However, in the pathomorphological and instrumental imaging methods of studying these granulomatosis, attempts were made to identify various criteria for their differentiation (presence of caseous necrosis in PT, absence of caseous necrosis in PS, presence of peribronchial lymph nodes on intrabronchial ultrasonograms of peribronchial lymph nodes of a clear contour, conglomerates, absence of necrosis, and presence of septal vascular) [9, 49]. Nevertheless, the significance of these criteria is relative, and even a detailed pathomorphological analysis in about 10% of cases does not correct diagnosis because fibrinoid and even limited caseous necrosis can be observed in sarcoid granulomas, and perifocal nonspecific inflammatory changes may be absent in the granuloma circumference [5]. In support of this, we refer to the classic article on the pathomorphology of PS, which postulates the existence of an intermediate characteristics of the "poles" between classical PT and PS of the nosological form – necrotizing sarcoid granulomatosis [74].

Hans Selye (1907–1982) emphasized that diagnosticians and pathologists find diseases interesting for their differences and similarities, respectively [22]. Currently, the role of MBT or any other microbial or nonmicrobial agents as the main causative factor in sarcoidosis has not been proven. However, the concept of tuberculosis and sarcoidosis as two variants of the response of the body's reactivity to close or even identify etiological factors (possibly against a different mosaic-permissive background of polyetiologically interacting groups of causal factors, reactivity, and external conditions) is not rejected and finds supporters, including in the literature of the latter years [35, 64, 65].

Hormones are the most important tools for the deployment and regulation of reactivity [32]. In our opinion, comparisons of the state of vitamin D and prolactin metabolism in PS and PT may be promising, considering the differences in the spectrum and intensity of autoimmune reactions and the cytokine profile in these diseases. We performed such a pilot analysis and found an increase in the active form level of vitamin D calcitriol only in PS and prolactin only in tuberculosis, coupled with many common and different features of autoimmunity and cytokine profile against the background of a low cathelicidin response in both diseases [27, 38]. The overproduction of the active form of vitamin D in sarcoidosis can be regarded as a manifestation of a protective response of the immune system to an unknown pathogen, providing

a relatively favorable course of granulomatous inflammation compared with tuberculosis [37], due to the known stimulating effect of this vitamin on anti-infectious immunity [63].

Thus, although PS is less common than PT due to an increase in morbidity, mortality dynamics, and new provoking factors, including iatrogenic ones, the importance of its study is increasing [49, 50, 66, 67].

New challenges facing the healthcare system do not cancel old problems. For example, in the context of a pandemic of the new COVID-19 infection, the question of its interaction with sarcoidosis is relevant, which is actively raised in the literature in 2020 [83] but has not been studied. In our opinion, despite the obvious answer (PS would seem to aggravate COVID-19 and PS immunotherapy could facilitate infection), it can have unexpected, paradoxical aspects; for example, it is possible that, in a typical case, patients with increased disease marker and ACE levels in the blood [5, 29, 33] will be less susceptible to COVID-19, as this can competitively hinder the penetration of the virus through the receptor (ACE2) it uses into target cells. Calcitriol production in granulomas of sarcoidosis may also work in favor of protection against COVID-19 [38]. A development case of sarcoidosis granulomas in the recovery phase of the coronavirus pneumonia has been described, and it is interpreted by the authors precisely as a manifestation of the body's defense reaction [36].

## CONCLUSION

Since the 1970s, despite the differences of PS and PT and their completely different epidemiological danger and unequal prognosis for life, many researchers have tried bringing the clinical pathophysiology of tuberculosis and sarcoidosis closer together as granulomatous diseases based on chronic inflammation controlled by mechanisms of delayed-type hypersensitivity with the participation of autoimmune reactivity [4, 40, 47, 59, 77]. At the same time, in several patients with sarcoidosis, components of mycobacteria were found in the lesions, and evidence of an immune response was found in the blood, which was the reason for prescribing antituberculosis therapy [9, 31, 79].

In this regard, we emphasize that granulomatous inflammation is a compromise of the adaptive strategies of the pathogen and macroorganism; therefore, with different immunoreactivities (and nonidentical conditions), the same causal factors can generate a whole spectrum of responses – from typical caseous-necrotic granulomas in PT to non-necrotic granulomas in light PS. The progress in understanding the ratio of these forms of pathology will be determined by the abovementioned new PS models [53, 72, 77] and the study of the regularities of polarization of macrophages and their signal-metabolic responses in PS and PT.

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