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Radiation Patterns of Modern Sarcoidosis (Alphabet)

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Abstract

Radiation diagnostics of sarcoidosis in modern conditions is CT, supplemented by radionuclide studies (SPECT, PET), ultrasound, MRI. The paper describes the classic signs of pulmonary sarcoidosis (according to the Statement on Sarcoidosis, 1999), which have changed their characteristics due to the widespread use of CT: variants of lymphadenopathy, dissemination, interstitial involvement. New unfavorable forms of thoracic sarcoidosis are discussed: fibrous sarcoidosis (with a description of the variants of sarcoid fibrosis and their differences from other progressive pulmonary fibrosis) and progressive sarcoidosis (possible causes and patterns). Radiation semiotics of extrapulmonary and comorbid manifestations is touched upon.

Keywords: pulmonary sarcoidosis, systemic sarcoidosis, comorbidity in sarcoidosis, radiation diagnostics, computed tomography

1. Introduction

Sarcoidosis is a polysystemic inflammatory disease of unknown etiology, related by its morphological characteristics to the group of lymphotropic granulomatosis with the formation of noncaseating granuloma, most often the disease reveals, itself as pulmonary sarcoidosis (PS) manifestations [1, 2]. The clinical and radiation symptoms of PS are well studied and defined by the American Thoracic Society (ATS), the World Association for Sarcoidosis and Other Granulomatous Diseases (WASOG), the European Respiratory Society (ERS) and the Russian Respiratory Society [2–4]. On the basis of the traditional X-ray picture of the process, Scadding J.G. [5], identified 5 stages of PS, which are used to this day, in a modified version of the assessment by computed tomography (CT). In recent decades, due to the widespread use of CT in patients with PS, there have been revealed changes in the lungs that are not characteristic of this disease and go beyond the stages of its generally accepted radiological classification. According to various authors, the frequency of atypical forms of PS varies from 2–25% or more of all detected cases [6, 7]. In recent decades, there has been an increase in the number of cases of atypical and progressive variants of the course of sarcoidosis, including the formation of fibrosing sarcoidosis of the lungs, damage to vital organs (kidneys, heart, central nervous system) requiring transplantation, and an increase in mortality from sarcoidosis [8, 9]. The ineffectiveness of the treatment has led to the identification of a separate form - refractory sarcoidosis [10]. Most often, sarcoidosis is treated by pulmonologists (since the main manifestation of the disease is PS), a thoracic radiologist who is well aware of the radiation semiotics of disseminated lung processes works with them. However,

sarcoidosis is systematic, which requires a pulmonologist to know about possible variants of damage to other organs and systems, and from a radiologist about the radial signs of their damage, the ability to analyze multimodal studies and draw up an optimal radiation algorithm to identify all systemic changes [11]. The incidence of organ damage in sarcoidosis varies across studies, which makes these figures not very reliable (this is probably due to the use of hospital design in most studies, which includes patients with sarcoidosis observed in certain clinics; studies using population design, based on national or regional registers are considered to be the best). It is clear that the likelihood of extrathoracic lesions is very high and underestimated, since they are mostly favorable, asymptomatic (like most of the PS). Isolated extrathoracic lesions in sarcoidosis are very difficult. They mimic various diseases, are poorly recognized without the support of a pulmonologist, are confirmed only morphologically, are often the reason for multiple revisions of morphological data (they will not be considered in this study). The multisystem nature of the lesion can lead to a significant decrease in the patient's quality of life [3]. Extrathoracic lesions in sarcoidosis require additional examination under the supervision of a physician of the relevant specialty. Now, the criteria for cardiosarcoidosis and neurosarcoidosis have been published; there are no clear recommendations on the volume and methods of radiation studies in other localizations. Thus, in general clinical practice in the absence of symptoms, a basic eye examination is proposed for screening ocular sarcoidosis, a basic serum creatinine test for screening renal sarcoidosis, a serum alkaline phosphatase test for screening liver sarcoidosis, an ECG for detecting possible heart damage [4]. In determining the typical radiation semiotics of damage to various organs in sarcoidosis, the structured Delphi methodology is used, when the agreement of more than 70% of experts allows a consensus to be reached. This is necessary because a radiologist should be a member of a multidisciplinary team dealing with a patient with sarcoidosis, know the clinical manifestations, possible variants of systemic damage and the optimal radiation algorithm for examining patients with different risks.

While proceeding clinically favorably, sarcoidosis does not really bother the patient, however, comorbid lesions (neoplasms, infectious processes, PE) change both the clinical picture of the disease and its radiation signs [12, 13]. The different types of dissemination seen on CT scan suggest a comorbidity is present. To simplify the assessment of systemic damage in sarcoidosis, attempts have been made to create diagrams that simplify the diagnosis. So, in the work of Schupp J.C., et al. [14], five clinical clusters of sarcoidosis were proposed: (1) damage to the abdominal organs, (2) damage to the eyes, heart, skin and central nervous system, (3) damage to the skeletal muscle and skin tissue, (4) involvement of the pulmonary and intrathoracic lymph nodes, and (5) extrapulmonary involvement. In 2014, the World Association for Sarcoidosis and Other Granulomatous Diseases (WASOG), according to the Delphi study, proposed a probability scale [15]: certain: the likelihood of sarcoidosis causing this manifestation is at least 90% (e.g.: uveitis, bilateral hilar lymphadenopathy, perilymphatic foci on chest CT); probable: the probability of sarcoidosis is 50–90% (for example: paralysis of the seventh cranial nerve, edema of the lacrimal gland, localization of the process in the upper lobes or diffuse peribronchovascular infiltrates); possible: the probability of sarcoidosis is less than 50% (for example: arthralgias, localized infiltration on radiographs). However, in practice, the use of these criteria is not always convenient. Studies in systemic and comorbid sarcoidosis suggest radiation multimodality (MRI, PET, SPECT, 67 Ga scintigraphy), however, CT with its various techniques (HRCT, functional tests, CT angiography) remains the main and at the same time expert method for its diagnosis, which allows and qualitatively answer the questions of the pulmonologist. The article discusses the changes detected during routine CT examination of patients

with sarcoidosis, to which a radiologist should draw the attention of the pulmonologist. These findings can change the tactics of patient management and require additional radiation studies.

2. Radiation patterns of modern sarcoidosis (alphabet)

We analyzed the data of radiological studies of 873 patients observed with a diagnosis of sarcoidosis from 2006 to 2021 at the St. acad. I.P. Pavlova. The observation period ranged from 6 months to 22 years. The average age of the patients was 47.2 ± 10.2 years (f / m - 500/373). All patients underwent CT, a pulmonary function tests (PFTs), and echocardiography, in some patients, if necessary, additional radiation studies (MRI, PET, SPECT) were performed. CT data revealed a number of radiation signs of typical (determined by WASOG) and not contradicting (probable and possible by WASOG) PS, which a radiologist needs to know to interpret radiation data correctly. The typical nature of the lesion suggests the possibility of making a diagnosis without biopsy (since even the most benign biopsy options are not desirable due to the development of scars at the site of the surgical injury and the likelihood of a decrease in FVC and DLCO). Radiation signs that do not contradict the manifestations of sarcoidosis require the convening of a multidisciplinary council and a decision to conduct histological verification, atypical radiation manifestations need to be supplemented with morphology. An analysis of the results of radiation research revealed the following radiation features of modern PS:

The defeat of the intrathoracic lymph nodes: typical (58.6%) were symmetrical lesions of the peritracheobronchial, paraaortic, intrapulmonary groups (with the obligatory involvement of bronchopulmonary lymph nodes), the absence of necrotic changes in the structure, the preservation of the integrity of the lymph node capsule, the preservation of the surrounding cellular spaces (**Figure 1a**), the absence of compression adjacent vessels and bronchi even with a large increase in lymph nodes (**Figure 1c**), uniform accumulation of contrast agent in them during all phases of intravenous bolus contrast enhancement (**Figure 1a**) and high metabolism of 18FDG on PET (**Figure 1b**). Not contradicting the diagnosis of sarcoidosis is the presence of calcifications in the structure of the lymph nodes (25.2%) (**Figure 1d**), the asymmetry of their lesions (5.0%) (**Figure 1e**), the lesion of non-characteristic groups (retrosternal, paraesophageal) in combined with the defeat of typical groups (2.3%) (**Figure 1f**).

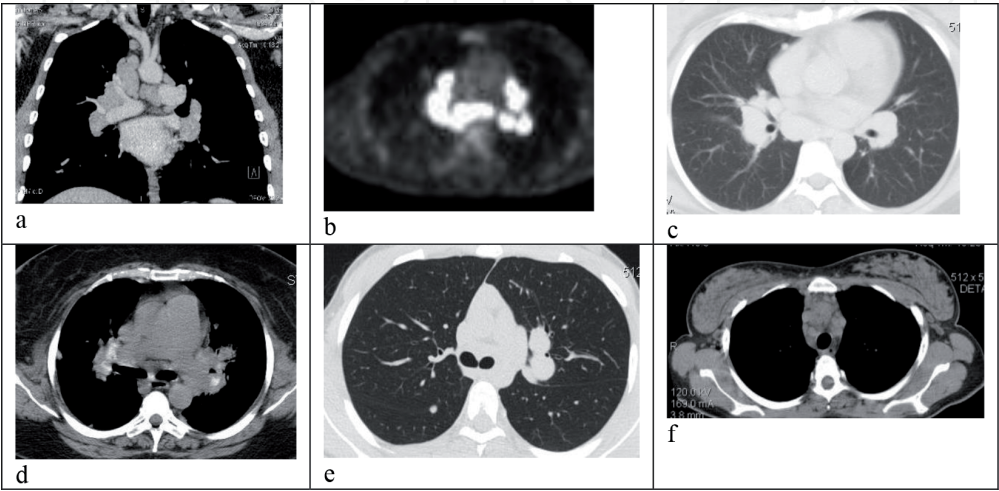


Figure 1.
Radiation picture of the defeat of the lymph nodes with PS (explanations in the text).

Lung lesion with PS consists of two components: the presence of foci and lesions of the interstitium. **Perilymphatic foci were typical** - small (up to 3 mm), of the same type, along the interlobular septa, along the bronchi, vessels, pleura (46.3%) (**Figure 2a**), large foci of irregular oval or trapezoidal perilymphatic arrangement (67.0%) (intrapulmonary lymph nodes), which regressed more slowly than other foci (Figure 2b), fusion of small foci into large ones with indistinct contours (17.1%) (symptom of “galaxy”) (**Figure 2c**), fusion of foci into peribronchovascular masses - sarcoids (11.9%) (**Figure 2d**). Not contradicting the diagnosis of sarcoidosis is the identification of flat subpleural foci (2.2%) (plaques) (**Figure 2e**), and the presence of calcifications in the foci (1.2%) (**Figure 2f**). The presence of cavities in the foci (0.2%) also did not contradict the diagnosis of sarcoidosis: Patient A., 23 g. 2008 (**Figure 2g**) - typical intrathoracic lymphadenopathy,

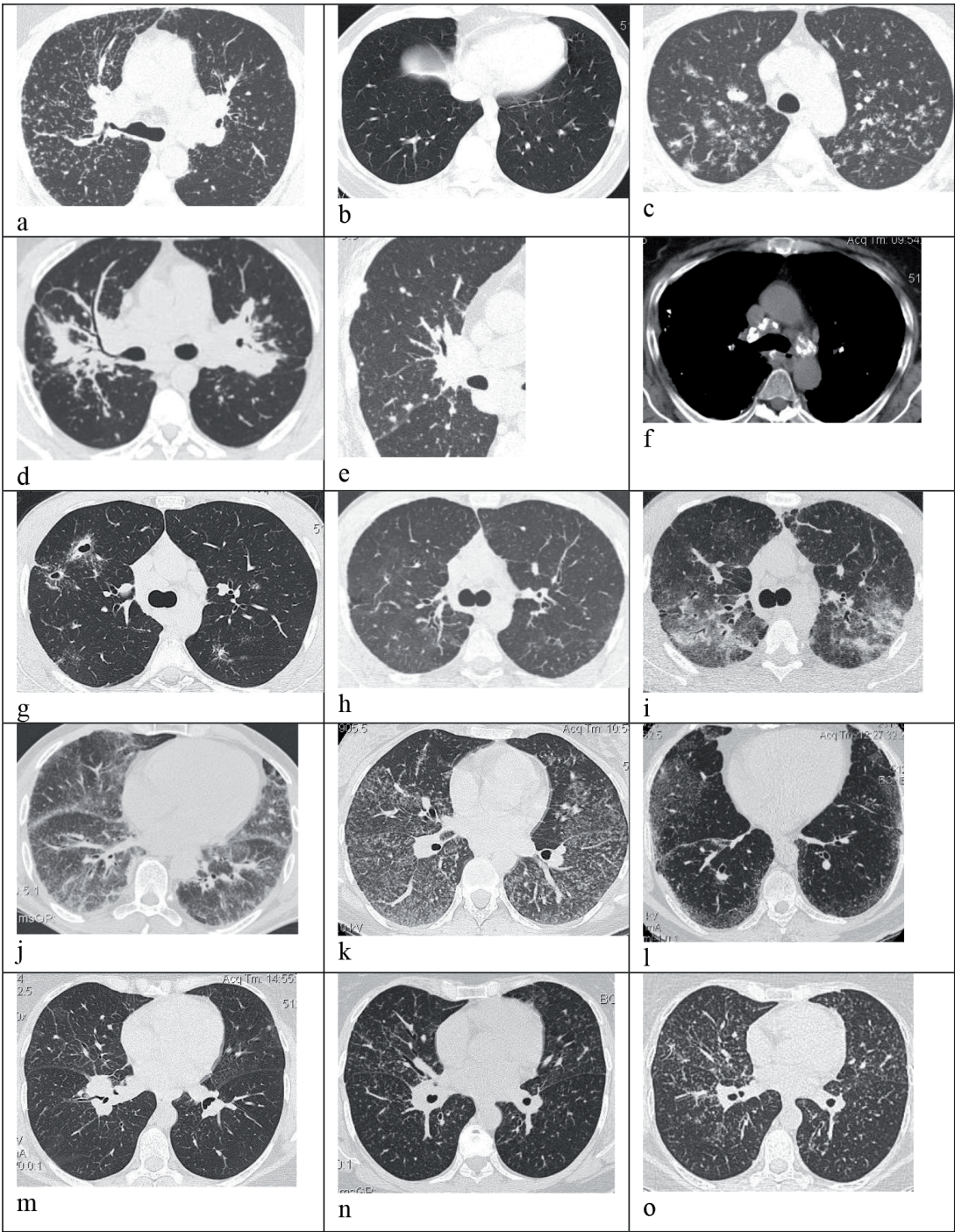


Figure 2.
Radiation picture of lung lesions with PS (explanations in the text).

perilymphatic dissemination with the formation of a symptom of “galaxy”, cavities in the foci, 2011 (**Figure 2h**) - regression after steroid therapy with preservation of post-sarcoid perilymphatic fibrous foci, 2013 (**Figure 2i**) progression of the process: an increase in perilymphatic dissemination, edema of the peripheral pulmonary interstitium, the formation of sarcoids. **The lesion of the interstitium** in sarcoidosis can be both of temporary (edema, cell infiltration) and of permanent character (fibrosis) character. Sarcoidosis is characterized by a lesion of the central interstitium with the presence of peribronchovascular “couplings” and sarcoids, damage of the peripheral interstitium (thickening of the interlobular - the wall of the secondary pulmonary lobe and intralobular - acinar septa) is not typical and is an unfavorable symptom that predicts a high likelihood of developing respiratory insufficiency at advanced stages. **Manifestations of sarcoid alveolitis** (10.2%) - compaction of the peripheral pulmonary interstitium of the “ground glass” type, due to the presence of edema and cellular infiltration before the formation of granulomas (**Figure 2j**), or the presence of small perilymphatic foci in the wall of the alveoli (**Figure 2k**) with the possibility of forming fibrosis of the peripheral interstitium (**Figure 2l**). Persistence and increase in edema of the peripheral pulmonary interstitium in sarcoidosis is an unfavorable scenario for the development of the disease, leading to the formation of interstitial fibrosis: Patient K., 49 years old. 2016 (**Figure 2m**), 2018 (**Figure 2n**), 2020 (**Figure 2o**), the progression of the process: regression of lymphadenopathy, an increase in perilymphatic dissemination, edema of the peripheral pulmonary interstitium with the formation of fibrosis, in 2020. - the appearance of shortness of breath, dry cough, a decrease in DLCO to 68% of D. Not contradicting the diagnosis of sarcoidosis is the asymmetry of the lesions of the lung tissue and interstitium (7.2%) (**Figure 2a**).

The transition of PS in stages III and IV is accompanied by fibrosis processes (which, in a number of patients, requires the inclusion of the disease in the category of progressive pulmonary fibrosis). Typical are **fibrotic changes** in the central pulmonary interstitium (at the sites of granuloma localization) with the formation of peribronchovascular fibrous couplings (4.7%) (they differ little from sarcoids, which can regress; within 6 months) with the formation in these areas of traction bronchiectasis of large bronchi (since these are the basal regions), a decrease in the volume of the upper and middle pulmonary fields, in contrast to IPF, in which the lower lobes are more affected. The type of pulmonary volume reformatting is better seen when constructing image reformation (MPR, MinP). Calandriello L., Walsh S.L.F. [16] suggest that posterior displacement of the main or upper lobe bronchus with a decrease in the volume of the posterior segments of the upper lobes is a typical feature of fibrous sarcoidosis. The volume of fibrosis of the lung tissue in stage IV PS is very different: minimal “gentle” fibrous changes of a linear nature (**Figure 3a**), peribronchovascular fibrous couplings (**Figure 3b**), massive peribronchovascular fibrous changes, forcing to change the course of the vessels in the anterior regions to rounded (“vortex” symptom) (**Figure 3c**).

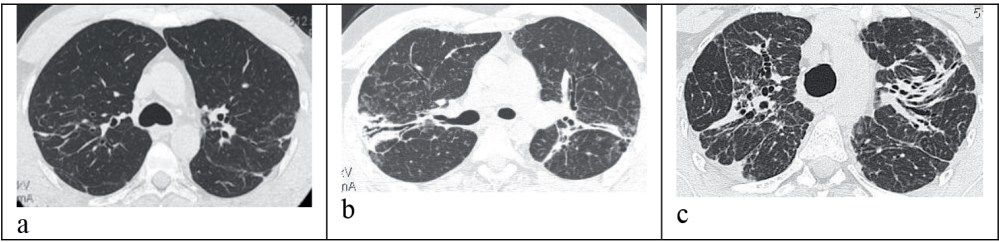


Figure 3.
Radiation picture typical fibrotic changes in PS (explanations in the text).

Not contradicting the diagnosis of sarcoidosis is the identification of a “honeycombing lung”, which is rarely observed (1.9%), has a short length and can be localized both in the subpleural and in the basal regions. Preservation of lymphadenopathy and perilymphatic foci is possible at III and IV stages of the disease. These forms belong to the unfavorable variants of the clinical course - fibrosing and progressive sarcoidosis. According to Xu L. et al. [17], in contrast to the “honeycombing” in the case of usual interstitial pneumonia (UIP), the “honeycomb” in PS is located centrally and is accompanied by traction expansion of large bronchi (bronchiectasis). It was noted that fibrous and active granulomatous patterns are present in the final stage of PS. Abehsera M. et al. [18] believe that two main models of fibrosing sarcoidosis of the lungs have characteristic radial and functional features: in peribronchovascular fibrosis, obstructive disorders in PFTs with a decrease in FEV1, an increase in OOL, with the formation of a “honeycombing lung” - restrictive disorders with PFTs with a decrease in FVC, DLCO. They also noted that progressive pulmonary sarcoidosis was characterized by the presence of chronic Aspergillus or bacterial infection. D. Valeyrea et al. [19] highlighted the same two main CT patterns of progressive pulmonary sarcoidosis with different functional profiles, noting that they may be with or without signs of activity, concluding that an algorithm based on pulmonary function and CT, allows predicting survival in progressive sarcoidosis. According to our data, 8.9% of patients had a severe course of the disease with dyspnea and radiation signs of fibrosis, which were not typical for the classical version of the course, the traditional radiation pattern and the existing X-ray classification of PS. Our analysis allowed us to identify several models of atypical pulmonary sarcoidosis.

Model of interstitial edema (IE): edema and cellular infiltration of the peripheral pulmonary interstitium (1.5%) was manifested by the presence of small perilymphatic dissemination, merging into a picture similar to the manifestations of interstitial pulmonary edema (clinically also similar to it - shortness of breath, dry cough). Perhaps the fibrous form of sarcoidosis is the outcome of the interstitial-edematous form in patients who did not receive adequate timely therapy, or the result of a comorbid course of sarcoidosis (with viral pneumonia, concomitant occupational pathology) (**Figure 4a**).

Model of idiopathic pulmonary fibrosis (IPF) - fibrosis of the peripheral pulmonary interstitium (1.0%): persistent CT-picture of “ground glass” opacity

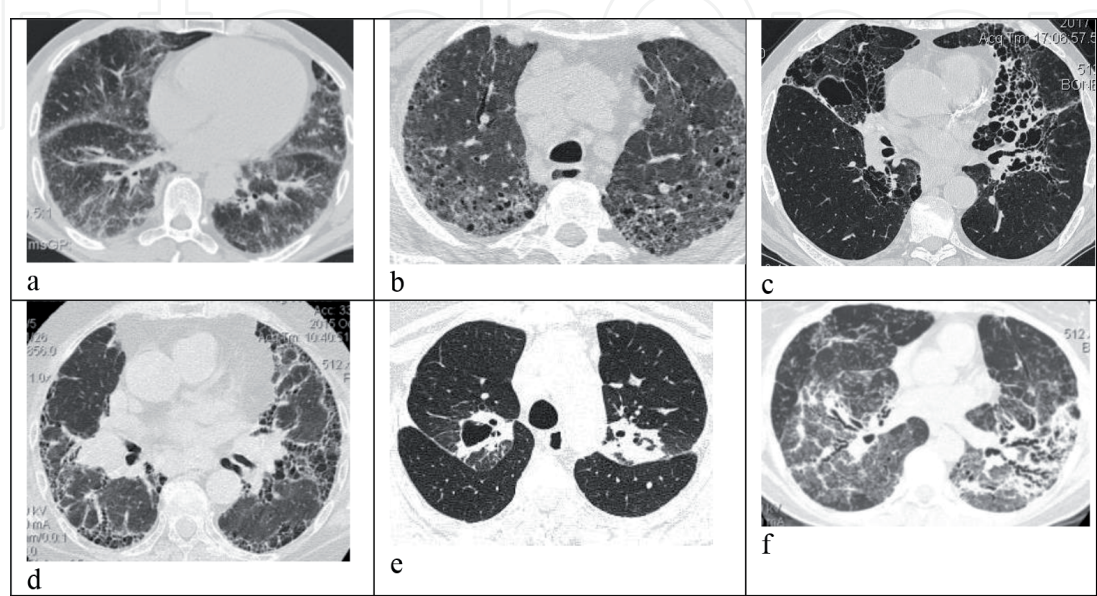


Figure 4.
Radiation picture of possible fibrotic changes in PS (explanations in the text).

(intralobular fibrosis), traction bronchiolysis, “honeycombing lung” in combination with lymphadenopathy of the peritracheobronchial groups. With the IPF model of sarcoidosis, there were noticed less severe than with IPF clinical symptoms (moderate dyspnea), a positive reaction to steroid therapy (probably as a result of regression of sarcoid granulomas that exist even at advanced stages of the process), moderate restrictive disorders in PFTs: decrease in DLCO to 55% of D, CT-signs of pulmonary hypertension (SDPA 30.3 ± 3.8 mm Hg). Morphological examination revealed manifestations of fibrosing lung disease (fibrosis of the alveolar septa, formation of a “honeycomb lung”) and sarcoid granulomas (**Figure 4b**).

Model of hypersensitive pneumonitis (HP) - fibrosis of the central interstitium (1.3%). In the areas of peribronchovascular fibrosis typical for PS, the presence of a “honeycomb lung” with “honeycombs” of a large size was noted. These patients were also characterized by a long-term slow decrease in DLCO (up to 65% of D) and the associated gradual deterioration of health with an increase in shortness of breath and dry cough (**Figure 4c**).

PP + IPF model - fibrosis of the central and peripheral interstitium (0.9%). Fibrosis and “honeycomb” in the upper-posterior basal regions were combined with the presence of “honeycomb lung” in the subpleural areas. Changes of this type were accompanied by pronounced clinical changes (shortness of breath, decreased exercise tolerance, dry cough), the formation of severe pulmonary hypertension (with an increase in systolic pressure in the pulmonary artery to 62 ± 17 mm Hg), a decrease in DLCO (up to 50% of D) (**Figure 4d**).

The model of pneumoconiosis is a fibrocavitary form of PS (1.1%). The formation of cavities in the “sarcoids” (as a result of trophic disorders, or secondary sarcoid vasculitis). The shape of the cavities is irregular, the wall is varied. In some patients, there was a rapid regression of the process when steroid therapy was prescribed. In some patients, the changes progressed. Clinically, it proceeded calmly in most of the patients, in a number of patients it was accompanied by hemoptysis (**Figure 4e**).

A model of progressive PS (3.0%) - a combination of all stages at the same time - lymphadenopathy of the peritracheobronchial groups typical for sarcoidosis, perilymphatic dissemination in the lung tissue, massive fibrous changes of a severe nature in the upper-posterior basal regions on both sides with the formation of traction bronchiectasis. Clinically, these patients had a chronic recurrent unfavorable course of the disease, with wave-like radial changes in the increase and regression of perilymphatic dissemination and lymphadenopathy, were steroid -dependent - more often they were not treated at all (**Figure 4f**).

According to M.H. Jeon, et al. [12], interstitial lung disease with pulmonary fibrosis and pulmonary hypertension was associated with increased mortality, with pulmonary fibrosis accounting for 9.0% of deaths in sarcoidosis. According to Sève P., et al. [20] fibrotic changes on CT in sarcoidosis correlate with PFTs, 6-minute walk test data (6MWT) and the results of the St. George respiratory questionnaire. Thus, a decrease in the ratio of the forced expiratory volume in one second (FEV1)/FVC may be associated with significant deformation of the bronchi, their stenosis due to fibrosis, due to diffuse bronchial granulomatosis, compression of the bronchi with a significant increase in the lymph nodes of the mediastinum, and as a result granulomatous bronchiolitis or bronchial hyperreactivity. Low DLCO values may result from diffuse parenchymal lesions or sarcoid alveolitis.

Calandriello L., et al. [21] write about new trends in the assessment of SP, pointing to new directions: attempts to assess the state of the lung tissue in sarcoidosis using artificial intelligence (radiomics), the wider use of low-dose CT and MRI programs of the chest.

The algorithm of radiation examination for sarcoidosis suggests performing CT to assess intrathoracic changes with the analysis of signs of damage to the organs of the upper abdomen included in the scan area (liver, spleen, lymph nodes, kidneys), supplemented by ultrasound of the abdomen, if necessary, CT examination of the chest and abdomen in the conditions of intravenous bolus contrast enhancement and the use of MRI, PET, SPECT with gallium as reserve methods for assessing the systematicity of the lesion and comorbidity. The decision to appoint additional radiation studies is made by a multidisciplinary council. According to Kobak S. [22], the prevalence of extrapulmonary sarcoidosis is up to 80%. However, it is not known how to assess the systemic nature of the lesion, because almost all patients have minimal extrathoracic radiation and clinical manifestations. It is believed that the skin, eyes, heart and musculoskeletal system are the most commonly affected organs after the lungs. There were reported rare lesions of the gastrointestinal tract and isolated cases of sarcoidosis of the prostate, bladder, bone marrow and thyroid gland. Multiple organ damage is always chronic and more severe, and can lead to a serious disability or potentially fatal consequences. At the same time, according to Jeon M.H., et al. [12], there is no data on a significant difference in PFTs indicators in patients with and without systemic manifestations. According to C.-W. Li, et al. [23], patients with PS and extrapulmonary lesions had more pronounced changes in CT examination in patients with stage II of PS. It is not known which of the combinations of PS and systemic manifestations are the most dangerous. According to our data, systemic lesion in PS is accompanied by changing the favorable course of the disease to a more severe one, symptoms of damage to other organs come to the fore, but the pulmonological multidisciplinary council continues to play a decisive role in the diagnosis. Thoracic changes are the most specific and make it possible to make a diagnosis, while extrathoracic changes may be similar to other processes. Most of the extrathoracic changes are clinically as favorable as classical PS and are detected by chance during additional studies (ultrasound, CT, MRI of the abdomen and pelvis). Others have a vivid clinical picture (neurosarcoidosis, sarcoid cirrhosis of the liver, sarcoid sialoadenitis, sarcoid uveitis), and some may manifest as sudden death (cardiac sarcoidosis). In all cases, the X-ray archive is very important, since at the time of extrathoracic symptoms, PS as a rule has already been deliquescent for some time and can be identified retrospectively, even if it was overlooked in the initial analysis. Numerous attempts have been made to combine the symptoms of damage to different organs in sarcoidosis [9, 11, 14, 22, 23]. According to our data, the most frequent X-ray findings during chest CT were extrathoracic lymphadenopathy and damage to the parenchymal organs of the abdomen.

Extrathoracic lymphadenopathy (7.3%): neck, axillary groups, abdomen, pelvis has always been combined, with intrathoracic changes, according to our data. The characteristics of lymph node lesions were the same as those of intrathoracic ones (multiplicity of affected nodes in the group, no violation of the structure and integrity of the capsule, uniform accumulation of contrast agent in all phases of contrast enhancement, including delayed, high metabolism of 18-FDG on PET). Patient N., 29 years old. Lymphadenopathy of the peritracheobronchial groups, perilymphatic dissemination in the lung tissue are typical manifestations of stage II PS (**Figure 5a**), lesions of the lymph nodes of the extrathoracic groups; axillary (**Figure 5a**), deep and superficial cervical groups on both sides (**Figure 5b**), celiac and retroperitoneal groups (**Figure 5c**).

The lesion of the parenchymal organs of the abdomen in sarcoidosis is a frequent accidental finding during CT of the chest organs, because the liver, spleen and kidneys are partially covered by the scanned area. **Spleen** lesion in sarcoidosis may appear as splenomegaly and localized changes. A study by Tetikkurt C., et al. [24] showed that diffuse spleen lesion was associated with PS and other extrapulmonary

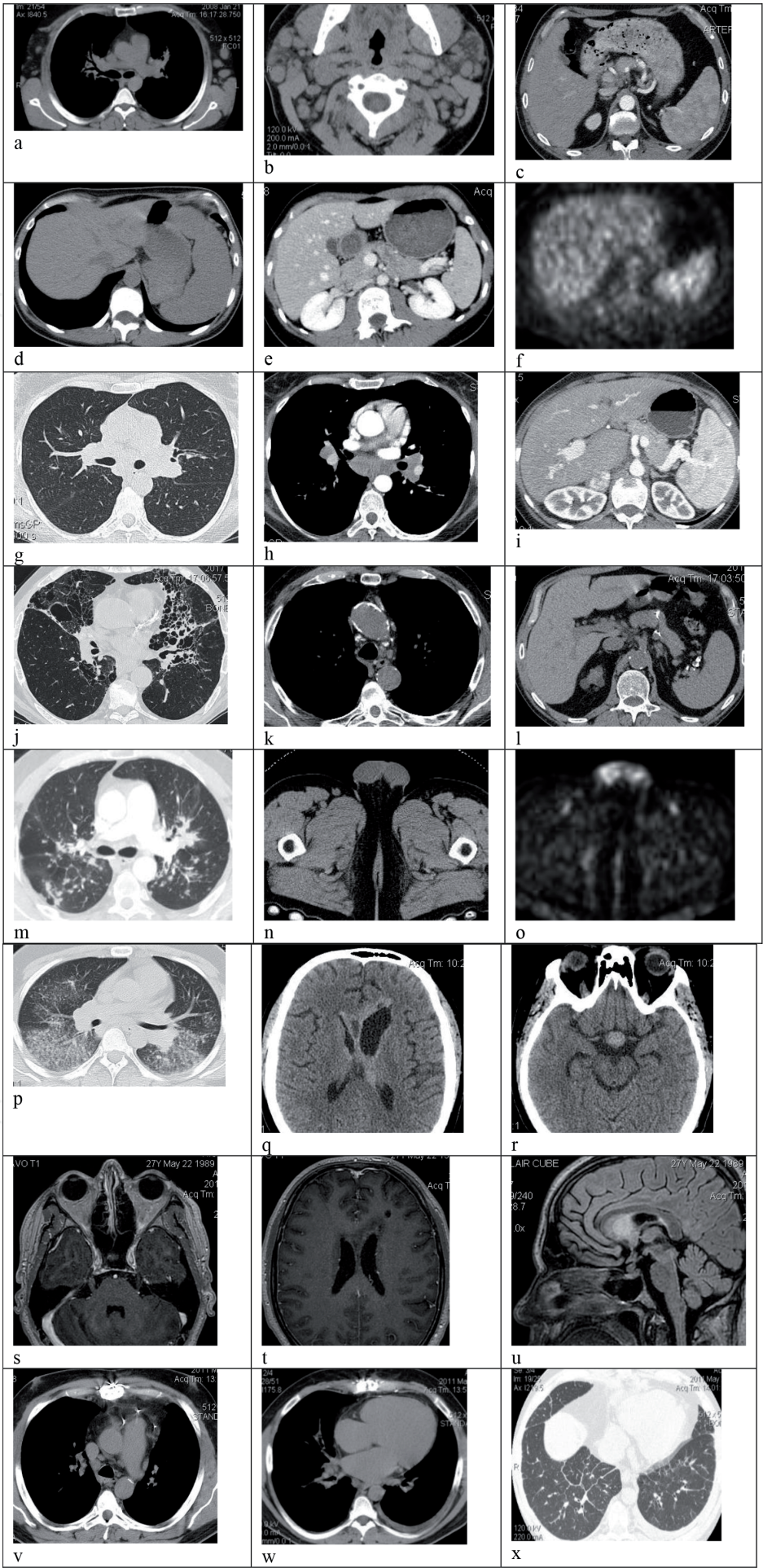


Figure 5.
Radiation picture of systemic manifestations in sarcoidosis (explanations in the text).

manifestations and appears to be a risk factor for chronic sarcoidosis. Changes in the blood count in sarcoidosis (leukopenia, lymphopenia, anemia, thrombocytopenia, and / or pancytopenia) increase the likelihood of bone marrow damage (rare) and the development of splenomegaly. According to our data, damage to the spleen was detected frequently (52.3%). The degree of enlargement of the spleen was different (up to hypersplenism - 2.0%), which could be an indication for splenectomy due to the risk of rupture and the appearance of clinical symptoms - dull ache in the left hypochondrium, shortness of breath, chronic fatigue. Even when the normal size of the spleen was maintained in one third of patients with sarcoidosis, PET showed an increase in the metabolism of 18-FDG, which was a sign of its granulomatous lesion. Rarely foci of low soft tissue density were detected in the spleen, accumulating contrast agent to a lesser extent than unchanged parenchyma (1.6%), regressing independently or during therapy, spleen infarctions (0.3%). The spleen lesion in sarcoidosis - hypersplenism (**Figure 5d**), foci in the spleen (**Figure 5e**), increased 18-FDG in the not enlarged spleen on PET (**Figure 5f**).

The liver is often affected in sarcoidosis. A meta-analysis by E.D. Crouser, et al. [4] showed that liver function tests in sarcoidosis patients were abnormal in 12% of patients, and among those who received a liver biopsy, granulomas were found in 96%. According to Tadros M., et al. [25], in biopsy and autopsy studies of patients with systemic sarcoidosis, liver involvement was found in about 50–80%, some patients may develop end-stage liver disease, and liver transplantation is required. it accounts for about 0.012% of the total number of liver transplants in the United States. P. Sève, et al. [20] note that portal hypertension occurs in 3 to 20% of cases of sarcoid hepatitis and may result from obstruction of the portal venous system due to significant enlargement of the lymph nodes of the hepatic hilum; the development of secondary ischemia, causing cirrhosis and focal fibrosis, or arteriovenous shunts, which increase portal blood flow. In our study, liver damage in sarcoidosis, as well as damage to the spleen, was most often asymptomatic and manifested by hepatomegaly (24.3%), which was accompanied by an increase in the metabolism of 18-FDG, foci of reduced soft tissue density that did not accumulate contrast agent (1.2%). A rare and tragic situation was the development of sarcoid hepatitis and subsequent cirrhosis, identified in 4 patients (0.4%) and manifested by diffuse changes in the liver parenchyma due to small and large-nodular rearrangements, hepatosplenomegaly, portal hypertension, ascites. To assess the progression of these changes, ultrasound elastography and MRI with intravenous contrast enhancement were also used. Patient Sh., 45 years old. Sarcoid cirrhosis of the liver, hepatosplenomegaly, portal hypertension. Lymphadenopathy (significant, symmetrical increase in peritracheobronchial groups, uniform accumulation of contrast agent in them, no signs of compression of adjacent vessels and bronchi), no changes in the lung tissue are typical manifestations of PS I st. (**Figure 5g** and **h**), an increase in the size of the liver and spleen, restructuring of the liver due to the presence of multiple nodes that unevenly accumulate contrast agent, hypertrophy of the caudate lobe are manifestations of sarcoid cirrhosis of the liver; expansion of the portal, splenic veins are manifestations of portal hypertension (**Figure 5i**).

E.D. Crouser, et al. [4] showed that **renal impairment** was detected in 7% of patients with sarcoidosis. Two mechanisms of renal dysfunction in patients with sarcoidosis are considered: parenchymal granulomatous inflammation and changes in calcium metabolism leading to nephrocalcinosis and nephrolithiasis. A meta-analysis by K. Al-Kofahi and P. Korsten [11] showed that 3.6% of sarcoidosis patients had nephrolithiasis at the first visit. They also described rare manifestations of kidney damage in sarcoidosis: pseudotumors or mechanical compression of the urinary tract by significantly enlarged lymph nodes with the formation of hydronephrosis. In our study, such forms of lesion were not identified, the revealed

changes were nonspecific: nephrolithiasis (2.8%), secondary renal wrinkling (as a result of a long course of tubulointerstitial sarcoid nephritis) (1.3%). Patient A., 61 years old, histologically verified sarcoidosis, fibrous form of PS IV st., neurosarcoidosis, chronic sarcoid tubulointerstitial nephritis: fibrous manifestations in the lungs that do not contradict PS: “honeycomb” formation in the hilar regions on both sides, minimal hilar lymphadenopathy (**Figure 5j** and **k**), wrinkling of the parenchyma of the left kidney partially included in the scan area (**Figure 5l**).

Polysystemicity presupposes the lesion of other organs, so, according to Lee J.K.T., et al. [26], an autopsy found sarcoidosis of the pancreas, intestines and testicles in 5% of patients. In our study, pancreatic sarcoidosis was suspected in 1 patient with increased metabolism of 18-FDG on PET, intestinal sarcoidosis was not detected, testicular sarcoidosis was an accidental finding during PET in 2 patients (0.2%) (increased metabolism 18 -FDG) and not manifesting clinically. Patient I., 46 years old. Systemic sarcoidosis. Lymphadenopathy of the peritracheobronchial groups, perilymphatic dissemination in the lung tissue are typical manifestations of SP II st. (**Figure 5m**), the absence of anatomical changes in the testes on CT (**Figure 5n**), high metabolism of 18-FDG in them on PET (**Figure 5o**).

Neurosarcoidosis occurs in 3–9% of patients with systemic sarcoidosis (in our study, in 1.1%). Its clinical manifestations are diverse, since any part of the nervous system (brain, meninges, cranial nerves, spinal cord, peripheral nerves) can be affected. CNS lesion predominates over PNS lesion; these lesions usually do not overlap. According to M. Ramos-Casals, et al. [27], systemic manifestations are characterized by a combination of damage to the eyes and the central nervous system, or a combination of damage to the liver and spleen and damage to the peripheral nervous system. According to Acharya N.R., et al. [28], ocular sarcoidosis was detected in 26% of patients with sarcoidosis, with anterior uveitis being the most common pathology (53%). Undoubtedly, the criteria proposed by Stern et al. [29], for a certain, probable and possible neurosarcoidosis will simplify the formulation of this complex diagnosis. Dierkes-Globisch A., et al. [30] showed a statistically significant trend towards a higher incidence of women in patients with CNS lesions and a higher incidence of kidney damage in patients with PNS lesions. Diverse radiation patterns in neurosarcoidosis require a multimodal and multidisciplinary approach. Patient M., 27 years old, complaints about general weakness, unsteadiness when walking, drowsiness, lethargy, rare dry cough, hearing loss in the left ear, thirst up to 5–9 liters per day, polyuria up to 9 liters per day. Lymphadenopathy of the peritracheobronchial groups, perilymphatic dissemination in the lung tissue are typical manifestations of SP II st. (**Figure 5p**). On CT, MRI (**Figure 5q–u**) - periventricular sarcoids (maximally around the anterior horns of the lateral ventricles, more on the left), pituitary sarcoidosis (with manifestations of diabetes insipidus and diabetes), trigeminal nerve on the right.

Cardiac sarcoidosis is an underestimated manifestation of sarcoidosis that can manifest as sudden cardiac death. According to Mehta D. et al. [31], screening for cardiac sarcoidosis includes cardiac MRI (CMR) and PET with 18 F-fluorodeoxyglucose (FDG-PET), ECG, echocardiography. It is noted that patients with delayed accumulation of gadolinium on MRI are at risk of adverse events, even with preserved left ventricular ejection fraction. According to Juneau D. [32], atrial involvement was seen in 9–50% cases of sarcoid. Birnie D.H. [33], notes that coronary arteries are usually normal, but extensive myocardial damage in sarcoidosis can lead to dilated cardiomyopathy. Radionuclide imaging with gallium 67, thallium 201, technetium are alternative tests for diagnosing and monitoring cardiac sarcoidosis that are useful when MRI is contraindicated or unavailable [11]. Patient B., 47 years old, the disease debuted with recurrent pulmonary embolism, repeated infarctions of the anterior wall of the left ventricle with the formation

of a left ventricular aneurysm and the development of heart failure refractory to therapy. Six months later, during surgery - linear plasty of the left ventricular aneurysm and removal of the left ventricular thrombus, a biopsy of the left ventricular myocardium was performed, and histological examination revealed epithelioid cell granulomas. After 10 months from the onset of the disease, CT examination of the chest organs revealed borderline mediastinal lymphadenopathy and changes in the lung tissue characteristic of SP II st. (**Figure 5v-x**). Also, there is an expansion of the cavities of the heart, trunk (34 mm) and large branches of the pulmonary artery, manifestations of interstitial stagnation, left-sided pleural effusion - manifestations of cardiomegaly, pulmonary hypertension, heart failure.

The relationship between the radiation signs of **SP and comorbid processes** changes the radiation pattern of both diseases. The most common comorbid processes in sarcoidosis are COPD, neoplasms, infectious processes, IPF and PE. All these comorbid conditions can have manifestations of disseminated chest lesions, complicating the differentiation of these diseases [12, 13]. The most common comorbid pathology in SP is acute PE, recurrent PE (RTE) and pulmonary hypertension, which can be caused by both sarcoidosis itself and chronic embolism (CTEPH). According to E.D. Crouser, et al. [4], echocardiography reveals signs of PH (high systolic pressure in the pulmonary artery) in 29% of patients with sarcoidosis. In his systematic review, Baughman R.P., et al. [34], noted a relationship between PH and the severity of lung disease (a decrease in FVC and DLCO correlated with the degree of PH). This is supported by S. Kobak [22], who noted that in patients with sarcoidosis, DLCO <60% may be a predictor of pulmonary hypertension. At the same time, according to P. Sève, et al. [20], increased pulmonary pressure may be associated with the sarcoid lesion itself: granulomatous lesions of the pulmonary vessels, a consequence of infiltration of the pulmonary parenchyma or compression by enlarged lymph nodes of large branches of the pulmonary artery in the mediastinum.

Acute PE, detected in our study in 3.3% of patients, caused the development of lobular pulmonary infarctions. Such changes can simulate a disseminated process (including sarcoidosis), conceal and be concealed behind sarcoid perilymphatic dissemination: patient K., 57 years old, SP III st., complicated by PE, a marker associated with a decrease in fibrinolytic activity. Multiple contrasting defects of the branches of the pulmonary artery on both sides - thrombotic masses causing their dilation, dilatation of the trunk of the pulmonary artery and its large branches - manifestations of PH (**Figure 6a**), perilymphatic dissemination characteristic of sarcoidosis and lobular infarctions of the lung characteristic of acute PE (**Figure 6b**), the source is a thrombus in the inferior vena cava (**Figure 6c**).

Pulmonary hypertension, often accompanied by IV st., fibrosing and progressive sarcoidosis and was detected in 7.3% of patients: patient D., 59 years old. Grade IV SP, CTEPH. Typical manifestations of SP IV st. are peribronchovascular fibrotic changes with the formation of traction bronchiectasis, volume remodeling with a decrease in the upper lobes and the formation of vascular torsion in the anterior regions - a "vortex" symptom (**Figure 6d**). Parietal contrast defect (long-term thrombotic masses) in a significantly dilated pulmonary artery trunk (**Figure 6e**). High degree of pulmonary hypertension: on a single CT scan, the aortic arch and the extended pulmonary artery trunk (**Figure 6f**).

The combination of sarcoidosis with neoplasms is rare (in our study - in 9 patients (1.0%). Combinations of sarcoidosis with various lymphoproliferative processes (lymphomas, leukemia), neoplasms of various localizations (which apparently are not related to each other), cancers are described. For example, Jamilloux et al. [35] note that lymphoma is a rare cause of death in sarcoidosis. Against the background of perilymphatic dissemination, it is difficult to identify

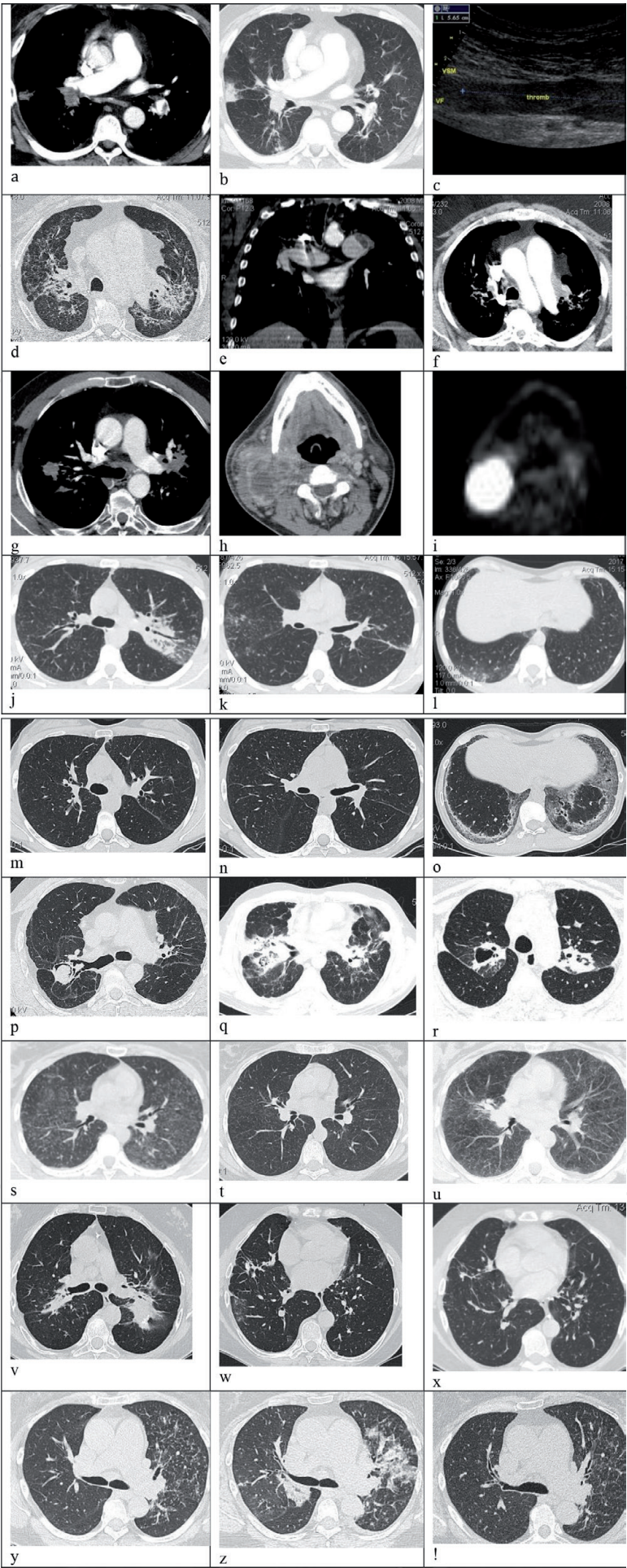


Figure 6.
Radiation picture of comorbid manifestations in SP (explanations in the text).

metastatic lesions, the basis of diagnosis is the hematogenous nature of the spread of metastases (we did not encounter the combination of sarcoidosis with lymphogenous metastatic lesions, perhaps it was not recognized due to the uniformity of the radiation pattern.) In 3 patients (0.3%) with a primary detected neoplasm, signs of sarcoid dissemination were determined, which could be due to the primary detection of sarcoidosis (finding) or a sarcoid reaction with some of the anti-cancer drugs. The use of PET did not help in this situation, because it increased metabolism of 18-FDG in sarcoidosis and oncological processes was equally high: patient I., 45 years old, chest CT - a typical picture of SP II st. - lymphadenopathy of the peritracheobronchial groups, peribronchovascular sarcoids (has had sarcoidosis since 2015, without significant X-ray dynamics) (**Figure 6g**). CT scan of the neck - conglomerate of lymph nodes of the middle deep cervical group on the right: large size, asymmetry, accumulation of contrast agent along the capsule with the presence of irregularly shaped necrotic masses in the center that do not accumulate contrast agent (**Figure 6h**), high metabolism of 18-FDG - poorly differentiated squamous cell cancer of the lateral wall of the oropharynx with secondary lymphadenopathy (**Figure 6i**).

The combination of **sarcoidosis with IPF** (and other progressive pulmonary fibrosis) is a rare, poorly understood situation. It is not clear whether the processes of fibrosis in the lung tissue are triggered by sarcoidosis itself, or whether these are two different diseases. As a rule, carrying out morphological verification also does not clarify the picture, since it identifies both sarcoid granuloma and signs of pulmonary fibrosis. Differential diagnosis with a fibrosing granulomatous process (hypersensitive pneumonitis) is also difficult, because it is often not possible to determine the cause of exogenous exposure. In our study, such a combination was found in 1.9% of patients. Patient V., 34 years old, histologically verified sarcoidosis. On CT from 2017 - perilymphatic dissemination (small foci, sarcoid on the left, manifestations of sarcoid alveolitis in the lower lobe on the right), lymphadenopathy of peritracheobronchial groups (**Figure 6j-l**). On CT from 2019. - multidirectional dynamics - regression of perilymphatic dissemination (traces in the form of small perilymphatic foci of a fibrous nature remain), an increase in interstitial changes in the lower-posterior subpleural regions on both sides - manifestations of progressive pulmonary fibrosis (**Figure 6m-o**).

For sarcoidosis, combinations with pulmonary inflammatory processes, both nonspecific and specific, are rare. The most common were the combination of sarcoidosis with COVID-19 lung damage (5.1%) and the formation of mycetomas in the sarcoid cavities (1.6%). The presence of **mycotic lesions** worsens the course of sarcoidosis due to toxic-allergic effects and the possibility of developing pulmonary hemorrhage. So, Jamilloux et al. [35], note that hemoptysis due to mycetoma can cause death in sarcoidosis. E. Criado, et al. [6], classifies sarcoidosis with manifestations of aspergillosis as an atypical radiation sign of sarcoidosis. The formation of mycetes in the fibrous sarcoid cavities with the appearance of symptoms of "sickle enlightenment" and "rattle" should force a pulmonologist to add antimycotic therapy: variants of mycetes in the sarcoid cavities (**Figure 6p-r**).

There is no increased risk of viral infection in sarcoidosis, however, during the COVID-19 pandemic, some patients with sarcoidosis have suffered this comorbid pathology. An analysis by Robert P. Baughman, et al. of five surveys of US and European survivors of sarcoidosis with COVID-19 [13] provided evidence that the incidence of COVID-19 infection in patients with sarcoidosis was higher than in the general population. They also noted that of the spectrum of immunosuppressive therapies taken by sarcoidosis patients, only rituximab was associated with an increased risk of COVID-19 infection. There was no association between prednisone intake and the development of COVID-19, regardless of the prescribed dose

(≥ 10 and < 10 mg / day). We have identified three main options for the combination of **COVID-19-sarcoidosis**: exacerbation of the course of sarcoidosis against the background of COVID-19 lesions; a combination of radiation signs typical of COVID-19 and sarcoidosis; accidental detection of PS against the background of COVID-19. In patients with sarcoidosis who are prone to developing pulmonary fibrosis, as well as in patients with IPF, COVID-19 could aggravate the course of the process and trigger the course of fibrotic changes.

Patient L., 43, histologically verified sarcoidosis. CT from 2014 (**Figure 6s**) - typical manifestations of PS with the presence of hilar lymphadenopathy and sarcoid alveolitis. CT scan from 2018 (**Figure 6s**) shows regression of the disease. On CT from 06.06.2020 (PCR on RNA SARS-CoV-2 (+) (**Figure 6u**) - bilateral edema of the peripheral and central pulmonary interstitium - CT picture of "ground glass" opacity - manifestations of sarcoid alveolitis overlapping small focal perilymphatic dissemination, lymphadenopathy of peritracheobronchial groups (significant, symmetrical, without violating the integrity of the capsule and the structure of the nodes) - exacerbation of sarcoidosis against the background of COVID-19.

Patient V., 68 years old, histologically verified sarcoidosis. CT scan from 2020 (**Figure 6v**) - typical manifestations of SP III st. with the presence of peribronchovascular fibrotic changes with the formation of traction bronchiectasis, moderate hilar lymphadenopathy, perilymphatic dissemination. Areas of interstitial infiltration in the subpleural regions on both sides - manifestations of COVID-19 lesions (PCR on RNA SARS-CoV-2 (+) (**Figure 6w**). On CT from 2019 (**Figure 6x**) changes characteristic of COVID-19 were not identified.

Patient A., 62 years old, histologically verified sarcoidosis. CT scan from 2019 (**Figure 6y**) - manifestations of SP II st. with the presence of perilymphatic small focal dissemination, hilar lymphadenopathy, PH. CT from 2020 (**Figure 6z**) - areas of interstitial and alveolar infiltration in the subpleural and nuclear regions on both sides - manifestations of COVID-19 lesion (PCR on SARS-CoV-2 (+) RNA. On CT from 2021 (**Figure 6!**) - regression of COVID-19 lesions, partial regression of perilymphatic dissemination and hilar lymphadenopathy, but an increase in signs of PH, fibrosis of the central and peripheral interstitium.

3. Conclusions

The sarcoid alphabet is an attempt to fully represent the radiation patterns of modern sarcoidosis in images from a to z with an explanation of their features and mechanisms of occurrence. Radiation diagnostics of pulmonary sarcoidosis is now a multimodal study with CT leading (as an expert technique) and supplementing, if necessary, radionuclide studies (SPECT, PET), ultrasound, MRI. Modern classical signs of SP (according to the Statement on Sarcoidosis, 1999) have changed their characteristics due to the widespread use of CT: variants of lymphadenopathy (features of the structure, localization of the affected lymph nodes), perilymphatic dissemination (manifestations of sarcoid alveolitis, types of foci), lesions pulmonary interstitium. Radiation patterns of unfavorable forms of SP were revealed: fibrosing sarcoidosis (with a description of the variants of sarcoid fibrosis and their difference from other progressive pulmonary fibrosis) and progressive sarcoidosis (with the identification of possible causes of its occurrence and radiation patterns). For the convenience of interpreting changes in SP detected by CT, we proposed models of unfavorable forms of SP: interstitial edema (IO), idiopathic pulmonary fibrosis (IPF), hypersensitive pneumonitis (PP), their combination, pneumoconiosis and progressive SP. It was noted that the model of interstitial edema in SP is often combined with multisystem lesions (eyes, kidneys), and has a high risk of

developing interstitial fibrosis (transition to the IPF model). The main points to which a radiologist should draw a pulmonologist's attention when performing a CT scan of the chest of a patient with sarcoidosis: describe all unfavorable models of sarcoidosis with the formation of fibrosis, expansion of cardiac cavities (indirect signs of cardiac sarcoidosis, especially in young patients, which requires MRI, or PET of the heart), signs of pulmonary hypertension (the causes of which may be vascular lesions in sarcoidosis and PE, which requires CT angiography, or SPECT), enlargement of the spleen (always within the scan area, may indicate additional hematological problems, both associated with sarcoidosis or not), identification of non-lymphotropic disseminations in sarcoidosis (a sign of comorbidity, requires CT in the whole body mode with multiphase contrast). Patients with sarcoidosis are seen by a pulmonologist and a thoracic radiologist, but the polysystemic nature of the lesion requires these specialists to know the signs of extrapulmonary manifestations of sarcoidosis (both clinical and radiation). If you suspect primary extrathoracic sarcoidosis (neurosarcoidosis, sarcoidosis of the kidneys, skin, eyes) in patients observed by doctors of other specialties, it is necessary to include not only a pulmonologist, but also a radiologist in the multidisciplinary consultation. Detection of radiation signs of comorbidity in sarcoidosis is especially important because it leads to a change in the tactics of patient management. The complexity of the layering of different types of pulmonary dissemination and lymphadenopathy and the multisystem nature of the lesion can be fully determined during a multidisciplinary consultation comprised of a pulmonologist and a radiologist with the involvement of an oncologist, neurologist, infectious disease specialist. The accumulation of experience in clinical and radiation examination of patients with sarcoidosis makes it possible to identify unfavorable clinical and radiological forms: fibrosing, progressive SP, as well as to assess its systemic manifestations and comorbidity, which is important for treatment tactics.

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Conflict of interest

The authors declare no conflict of interest.

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References

- [1] Il'kovich M.M. (Ed), Baranova O.P. Pulmonary sarcoidosis. In: Il'kovich M.M. Interstitial lung diseases.: GEOTAR-Media; 2016: 163-234 (in Russ).
- [2] Hunninghake G.W., Costabel U., Ando M., et al. ATS/ERS/WASOG statement on sarcoidosis: American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. *Sarcoidosis Vasc Diffuse Lung Dis.* 1999;16:149-173.
- [3] Saketkoo L. A., Russell A.-M., Jensen K., et al Health-Related Quality of Life (HRQoL) in Sarcoidosis: Diagnosis, Management, and Health Outcomes Diagnostics (Basel). 2021 Jun; 11(6): 1089.
- [4] Crouser E. D., Maier L. A., Wilson K. C., et al Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline *Am J Respir Crit Care Med.* 2020 Apr 15; 201(8): e26–e51.
- [5] Scadding J.G. Prognosis of intrathoracic sarcoidosis in England. A review of 136 cases after five years' observation. *Br Med J.* 1961;2:1165-1172.
- [6] Criado E., Sanchez M., Ramirez J., et al. Pulmonary sarcoidosis: typical and atypical manifestations at High-Resolution CT with pathologic correlation. *RadioGraphics.* 2010; 30: 1567-1586.
- [7] Shahram Kahkouee et al. Serum ACE Level in Sarcoidosis Patients with Typical and Atypical HRCT Manifestation// *Pol. J. Radiol.* 2016; 81: 458-461 (in Pol).
- [8] Cottin V., Muller-Quernheim J. Imaging of sarcoidosis of the airways and lung parenchyma and correlation with lung function. *Eur. Respir J.* 2012; 40: 750-765.
- [9] Belperio J. A., Shaikh F., Abtin F., Fishbein M. C., Extrapulmonary sarcoidosis with a focus on cardiac, nervous system, and ocular involvement *EClinicalMedicine.* Published online 2021 Jun 27.
- [10] Jammal T. E., Jamilloux Y., Gerfaud-Valentin M., Refractory Sarcoidosis: A Review *Ther Clin Risk Manag.* 2020; 16: 323-345.
- [11] Al-Kofahi K., Korsten P., Ascoli C. Management of extrapulmonary sarcoidosis: challenges and solutions *Ther Clin Risk Manag.* 2016; 12: 1623-1634.
- [12] Jeon M. H., Kang T., Yoo S. H., The incidence, comorbidity and mortality of sarcoidosis in Korea, 2008-2015: a nationwide population-based study *Sarcoidosis Vasc Diffuse Lung Dis.* 2020; 37(1): 24-26.
- [13] Baughman R. P., Lower E. E., Buchanan M., Risk and outcome of COVID-19 infection in sarcoidosis patients: results of a self-reporting questionnaire *Sarcoidosis Vasc Diffuse Lung Dis.* Published online 2020 Dec 16. doi: 10.36141/svdlld.v37i4.10726 PMID: 33597796
- [14] Schupp J.C., Freitag-Wolf S., Bargagli E., et al. Phenotypes of Organ Involvement in Sarcoidosis. *Eur. Respir. J.* 2018;51:1700991.
- [15] Judson M.A., Costabel U., Drent M., et al. The WASOG Sarcoidosis Organ Assessment Instrument: An Update of a Previous Clinical Tool. *Sarcoidosis Vasc. Diffus. Lung Dis.* 2014;31:19-27.

- [16] Calandriello L., Walsh S.L.F. Imaging for Sarcoidosis. *Semin. Respir. Crit. Care Med.* 2017;38:417-436.
- [17] Xu L, Kligerman S, Burke A. End-stage sarcoid lung disease is distinct from usual interstitial pneumonia *Am J Surg Pathol* 2013; 37(4):593-600.
- [18] Abehsera M, Valeyre D, Grenier P, et al. Sarcoidosis with pulmonary fibrosis: CT patterns and correlation with pulmonary function. *AJR Am J Roentgenol* 2000; 174:1751-1757
- [19] Valeyrea D., Nunesa H., Bernaudin J.-F. Advanced pulmonary sarcoidosis *Opin Pulm Med* 2014, 20:488-495
- [20] Sève P., Pacheco Y., Durupt F., Sarcoidosis: A Clinical Overview from Symptoms to Diagnosis *Cells.* 2021 Apr; 10(4): 766.
- [21] Calandriello L., D'Abronzio R., Pasciuto G. Novelties in Imaging of Thoracic Sarcoidosis *J Clin Med.* 2021 Jun; 10(11): 2222.
- [22] Kobak S. Catch the rainbow: Prognostic factor of sarcoidosis *Lung India.* 2020 Sep-Oct; 37(5): 425-432.
- [23] Li C.-W., Tao R.-J., Zou D.-F., Li M.-H. Pulmonary sarcoidosis with and without extrapulmonary involvement: a cross-sectional and observational study in China *BMJ Open.* 2018; 8(2): e018865.
- [24] Tetikkurt C., Yanardag H., Pehlivan M., Bilir M. Clinical Features and Prognostic Significance of Splenic Involvement in Sarcoidosis. *Monaldi Arch. Chest Dis.* 2017;87. doi: 10.4081/monaldi.2017.893.
- [25] Tadros M., Forouhar F., Wu G.Y. Hepatic Sarcoidosis. *J. Clin. Transl. Hepatol.* 2013;1:87-93.
- [26] Lee J.K.T., Warshauer D. M. Imaging Manifestations of Abdominal Sarcoidosis *American Journal of Roentgenology* January 2004, VOLUME 182NUMBER 1. 2004;182: 15-28.
- [27] Ramos-Casals M., Pérez-Alvarez R., Kostov B., Clinical characterization and outcomes of 85 patients with neurosarcoidosis *Sci Rep.* 2021; 11: 13735.
- [28] Acharya N.R., Browne E.N., Rao N., Mochizuki M. International Ocular Sarcoidosis Working Group. Distinguishing features of ocular sarcoidosis in an international cohort of uveitis patients. *Ophthalmology.* 2018;125:119-126.
- [29] Stern B.J., Royal W., Gelfand J.M., et al. Definition and consensus diagnostic criteria for neurosarcoidosis: From the Neurosarcoidosis Consortium Consensus Group. *JAMA Neurol.* 2018;75(12):1546-1553.
- [30] Dierkes-Globisch A., Schneiderhan W., Mohr H.H.. Acute renal failure due to hypercalcemia and peripheral polyneuropathy-rare manifestations of sarcoidosis. *Med. Klin.* 2000;95(10):583-586.
- [31] Mehta D., Lubitz S.A., Frankel Z et al. Cardiac involvement in patients with sarcoidosis: diagnostic and prognostic value of outpatient testing. *Chest.* 2008;133:1426-1435.
- [32] Juneau D., Nery P., Russo J. How common is isolated cardiac sarcoidosis? Extra-cardiac and cardiac findings on clinical examination and whole-body (18)F-fluorodeoxyglucose positron emission tomography. *Int J Cardiol.* 2018;253:189-193.
- [33] Birnie D.H. Cardiac Sarcoidosis. *Semin Respir Crit Care Med.* 2020;41(5):626-640.

[34] Baughman R.P., Engel P.J., Meyer C.A., et al. Pulmonary hypertension in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis.* 2006;23:108-116.

[35] Jamilloux Y., Maucourt-Boulch D., Kerever S., et al. Sarcoidosis-Related Mortality in France: A Multiple-Cause-of-Death Analysis. *Eur. Respir. J.* 2016;48:1700-1709.