CLINICAL OBSERVATIONS

Difficulties in the differential diagnosis of focal lung lesions in a patient with rheumatoid arthritis who has received anti-B-cell therapy with rituximab. Description of a clinical case

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We present a clinical case of a patient treated with rituximab and methotrexate for rheumatoid arthritis with progressive focal lung lesions that were difficult to interpret. The complexity of the problem of focal lung lesions in rheumatic diseases, which involves a broad spectrum of clinical medical disciplines, is emphasized.

Keywords: *rheumatoid arthritis; lung lesions; tuberculoma; methotrexate; rituximab; computed tomography of the lungs.*
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Focal formations in the lungs in rheumatic diseases require a complex differential diagnostic search due to the variety of clinical and instrumental manifestations and the lack of minimally invasive methods to make the correct diagnosis. The most accurate diagnostic method currently is a lung biopsy, however, the complexity of its implementation, as well as the risks associated with surgery, significantly limit the possibilities of its use.

A single, solitary pulmonary nodule (SPN) is defined as a spherical intrapulmonary mass with a well-defined margin, <3 cm in diameter, not associated with atelectasis, mediastinal lymphadenopathy, or pleural effusion, with possible calcification or cavitation [1]. In most cases, there are no symptoms, and characteristic signs are not usually detected by conventional radiography [2, 3]. SPNs are divided into solid and subsolid. All subsolid focal formations, in turn, are classified as pure "ground-glass" SPNs and SPNs containing solid components [2, 4, 5].

The differential diagnosis includes malignancies such as bronchogenic carcinoma, carcinoid tumors, lymphoma, and solitary pulmonary metastases, as well as various benign causes, including nonspecific granulomas, granulomatous infections, and hamartomas. Nowadays, most nodules can be visualized using computed tomography (CT scan), which greatly improves their detection and characterization.

Malignancy. In lung cancer screening studies of inpatients, the prevalence of malignancy was 0–1% for nodules <5 mm, 6–28% for nodules 5 to 10 mm, 33–64% for nodules 11 to 19 mm, and 64–82% >20 mm [4, 6]. Algorithms for a doctor's actions when detecting SPNs of different sizes are shown in fig. 1 (for nodules <8 mm) and fig. 2 (for nodules 8–30 mm).

Benign tumors. The most common benign solitary pulmonary nodules are infectious granulomas and benign tumors such as hamartoma, which account for approximately 10% of nodules found in the lungs [2, 5]. On radiographs they appear as SPNs with "popcorn" calcification, although this pattern occurs in less than 10% of cases. An effective method for diagnosing hamartomas is high-resolution chest CT (CHC), which allows to identify their typical visual signs: areas of fat and calcifications with layers of fat [7].

Less common types of SPN include vascular and inflammatory formations.

Vascular formations. In pulmonary arteriovenous malformations, contrast-enhanced CT allows visualization of the feeding artery and vein and distinguishes vascular formations from soft tissue ones. If pulmonary arteriovenous malformations with a feeding artery diameter >2–3 mm are suspected, CT with contrast and pulmonary angiography are recommended, and biopsy should be avoided. Less commonly, SPN of vascular origin can be represented by pulmonary infarction, rounded atelectasis, varicose veins of the lungs, and local hemorrhage [1].

Infection. In approximately 80% of cases, benign nodules are infectious granulomas [2, 5]. Endemic fungi (histoplasmosis, coccidioidomycosis) and mycobacteria are the most common etiological factors of infectious granulomas detected as SPN. Such lesions do not have pathognomonic signs, so most often they are diagnosed only after resection of the suspected tumor [8].

Other reasons. In rare cases, the formation of benign nodes may be associated with Wegener's granulomatosis, rheumatoid arthritis (RA), sarcoidosis, amyloidosis, folded lung syndrome, and perifissural lymph nodes [4].

Rheumatoid nodes (nodules) are among the most common extra-articular manifestations of RA, but they are rarely localized in the lung tissue. The development of extra-articular (systemic) manifestations of RA is associated with high concentrations of rheumatoid factor (RF) and antibodies to cyclic citrullinated peptide (ACCP). A peculiarity of rheumatoid nodes located in the lung tissue is their frequent occurrence with minimally expressed inflammatory changes in the joints or at the stage of remission. In addition, there are publications about the possible connection between the formation and

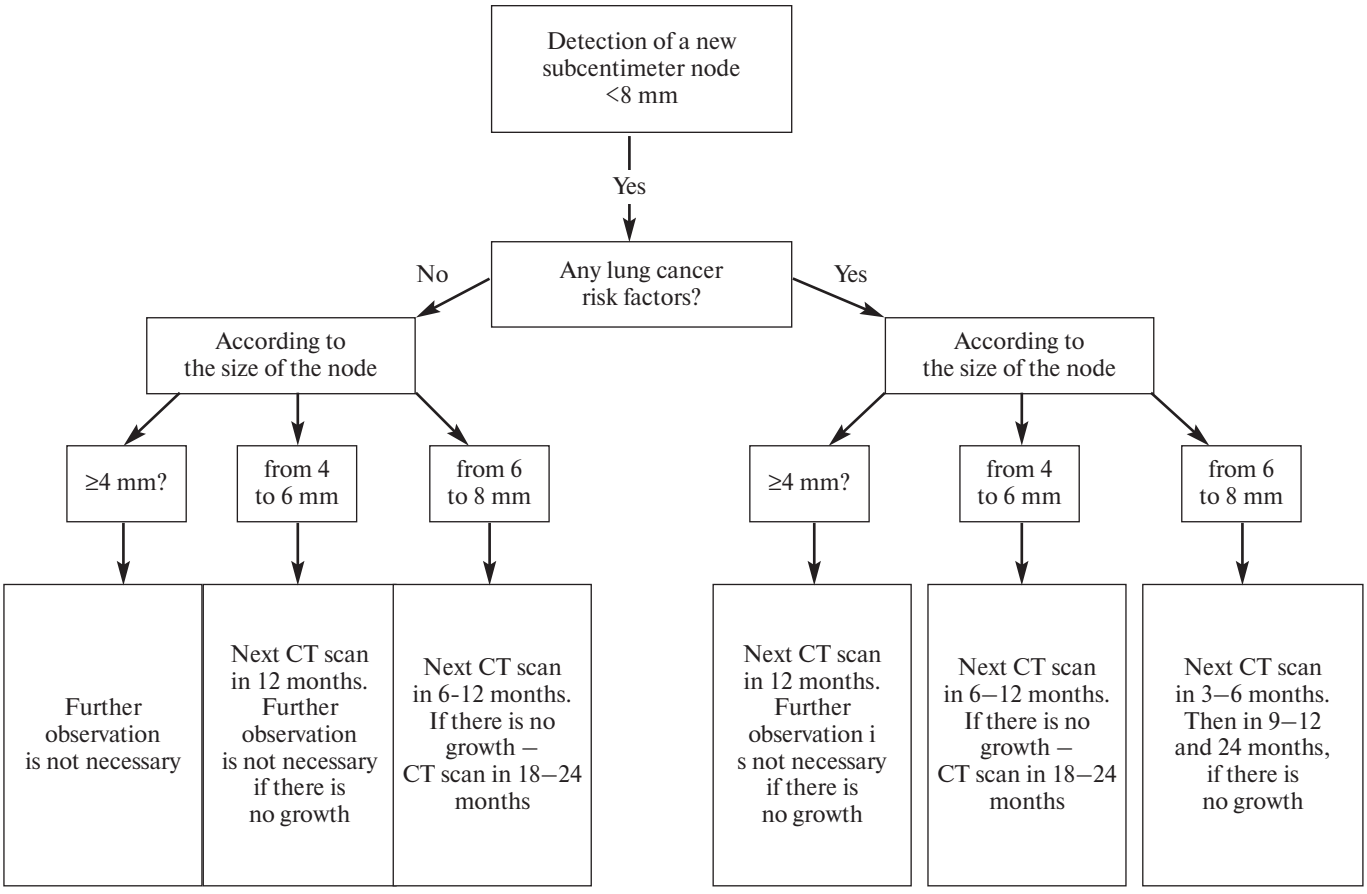

Fig. 1. *Plan of action when a new subcentimetre node (<8 mm) is detected [1, 4]*

acceleration of the development of rheumatoid nodes with the use of immunosuppressive drugs (methotrexate – MTX, – tocilizumab, D-penicillamine, gold salts, leflunomide, infliximab and other inhibitors of tumor necrosis factor α) [9].

We present a clinical observation of the progression of focal formations in the lungs in a patient with RA who received rituximab (RTM) and MTX.

Clinical observation

Patient A.*, a woman, 67 years old, was first hospitalized to the Federal State Budgetary Institution "Research Institute of Rheumatology named after. V.A. Nasonova" (NIIR named after V.A. Nasonova) in April 2022. The onset of the disease was in 2009 (at the age of 51 years) with symmetrical arthritis of the small joints of the hands, pain in the knee and shoulder joints, and morning stiffness. The disease was accompanied by high inflammatory activity, positivity for RF and ACCP. The diagnosis of seropositive RA was verified, meeting the criteria of the ACR (American College of Rheumatology) 1987 and ACR/EULAR (European Alliance of Associations for Rheumatology) 2010. She had previously received therapy with leflunomide, azathioprine, MTX, and sulfasalazine with insufficient effect. Before hospitalization, in December 2021, CT scan in the peripheral posterobasal parts of both lungs revealed numerous acinar nodes from 2 to 10 mm and micronodules, as well as nodes in S9, S10, areas of compaction in S8 on the right, discoid atelectasis in S5 on the left, considered as pulmonary manifestations of RA. It was recommended to carry out differential diagnosis with a specific process, pneumonia. She was consulted by an oncologist, a thoracic surgeon, and a phthisiatrician; no data were obtained in favor of a specific process or oncopathology.*

On admission, the number of painful joints was 6, the number of swollen joints was 2, ESR according to Westegren was 56 mm/h, CRP was 16.5 mg/L, RF was 512 IU/mL, ACCP was 142.1 U/mL, antinuclear factor (ANF) – 1/1280 sp, IgG – 6.2 g/L. Chest CT scan from April 2022: in the subpleural areas of the middle and lower parts of both lungs, areas of compaction of the lung tissue were identified as foci with a diameter of 5 mm and linear compactions with maximum dimensions of up to 28x6 mm. CT signs of atherosclerosis of the aorta and coronary arteries (Fig. 3).

On X-ray examination of the hands and distal feet, performed in April 2022, the picture was consistent with chronic erosive arthritis (Fig. 4, 5).

The diagnosis was confirmed: seropositive RA, late clinical stage, high activity (DAS28 – 5.57), erosive, radiological stage III, with systemic manifestations (rheumatoid nodes, interstitial lung disease with a decrease in the diffusion capacity of the lungs of moderate severity, DLCO – 56.9%). Sjugren's syndrome with damage to the salivary glands (xerostomia, sialadenitis morphologically verified in 2019) and lacrimal glands (keratoconjunctivitis grade 3), immunological disorders (ANF+, ACCP+), functional class 2. Joint damage came to the fore in the clinical picture. Lung nodules were considered to be systemic manifestations of the underlying disease. Due to the activity of RA and the absence of activation of tuberculosis infection (Diaskintest negative), RTM was prescribed at a dose of 1000 mg intravenously, and MTX therapy was resumed at a starting dose of 10 mg subcutaneously. Taking into account the

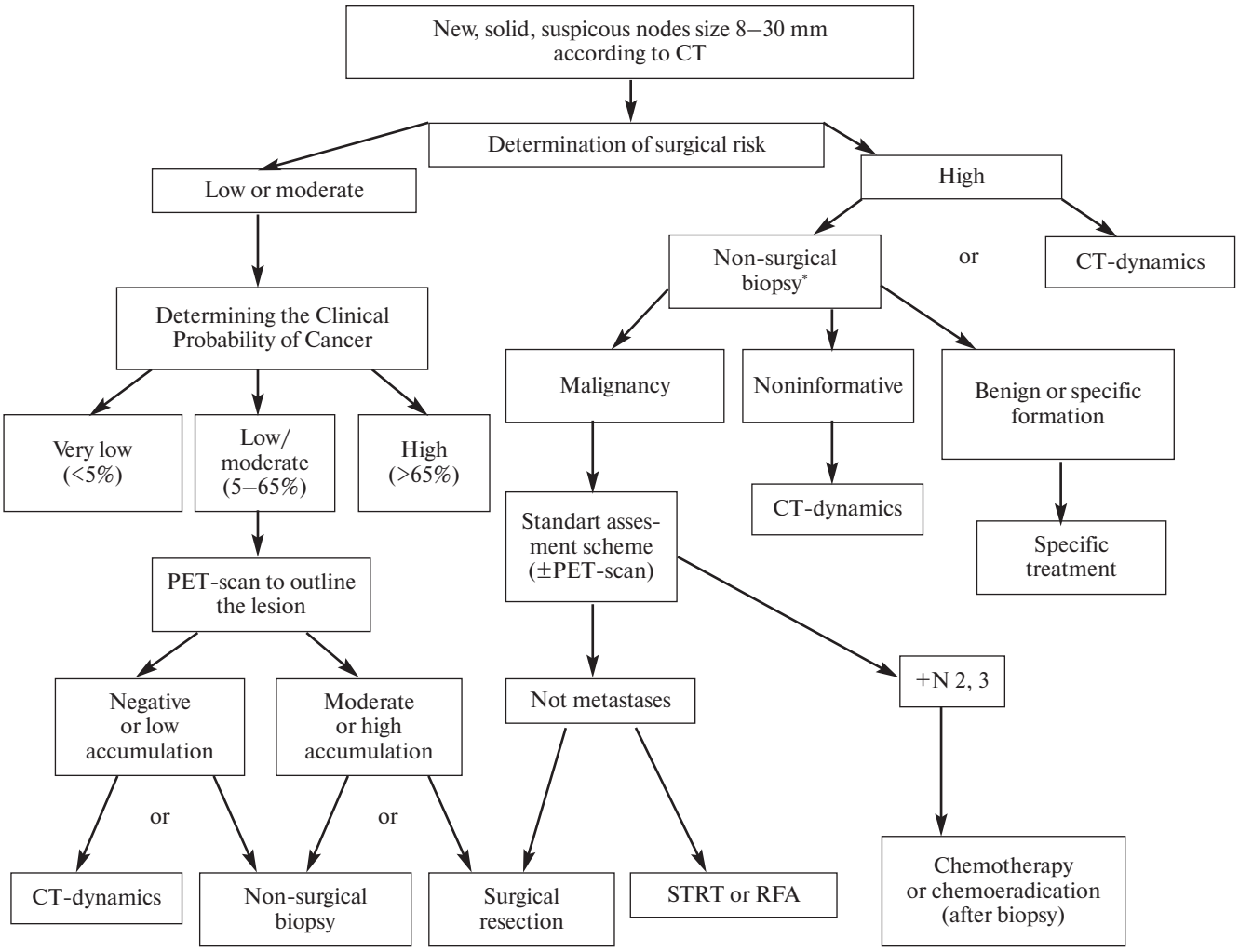

Fig. 2. *Plan of action when a new node with a diameter of 8–30 mm is detected [1]. *In patients at high risk of surgical complications, further observation using CT is recommended if the risk of malignancy is low or moderate, or non-surgical verification if the risk of malignancy is high. PET – positron emission tomography; STRT – stereotactic radiotherapy; RFA – radiofrequency ablation [4]; +N 2, 3 – number of affected lymph nodes*

presence of significant restrictions on hormonal therapy (osteoporosis, diabetes mellitus, glaucoma) and the stable condition of the patient, a dose reduction of prednisolone was started. During therapy, a decrease in pain, morning stiffness, and improvement in general well-being were noted. Subsequently, the patient received methylprednisolone 4 mg/day in combination with MT 10 mg/week and RTM every 6 months.

After 6 months, chest CT scan revealed an increase in the size of the nodes. Multiple solid foci were found in the parenchyma of both lungs; taking into account the data from the previous CT study and Lung-RADS II, rheumatoid nodes with a diameter of 3.7 mm (in S6 of the right lung) to 10 mm (in S10 of the right lung) seemed probable. Bronchiolitis-like changes were found in S6, S10 of the left lung. Disc-shaped collapse was detected in S5 of the left lung (Fig. 6).

A repeated consultation with an oncologist and a phthisiatrician was recommended. In April 2023, the third chest CT scan was performed (6 months after the second one). This CT showed in both lungs polysegmentally (more on the right) multiple (at least 30) round dense foci 3–22 mm in diameter, located perivascularly and subpleurally, the largest of which on the right were in S9/S10 – 15×17 mm (previously 8.9×11.1 mm) and 14×15 mm (previously 6.5×6.6 mm), in S4 subpleural – 15×12 mm (previously 8.4×9.2 mm), in S7 – 11.7×8.0 mm (previously 4x5.1 mm), on the left in S10 – up to 15×22 mm. The sizes of all other, smaller, lesions also increased. Single new lesions appeared in the right lung, up to 4–5 mm in size, which had not previously been visualized. In S7 on the right, in addition to the foci described above, small peribronchial focal-like structures were identified with the formation of a "tree-in-bud" pattern. In the upper lobe on the right there were single calcifications up to 3 mm. In the apices of the lungs, pneumatization of the parenchyma was uneven, "mosaic" due to areas of weakly expressed compaction of the parenchyma like "ground glass", alternating with areas of normal airiness. No pathological contents were detected in the pleural cavities. The trachea and bronchi were passable. Their walls were visually without any specific features. The mediastinum was not displaced, with normal structure. The heart was not enlarged. In the pericardial cavity there was a physiological amount of fluid. In the walls of the coronary and brachiocephalic arteries calcified atherosclerotic plaques were detected. There were no enlarged intrathoracic or axillary lymph nodes, degenerative-dystrophic changes in the spine. No bone destructive changes were found. Consolidated fractures

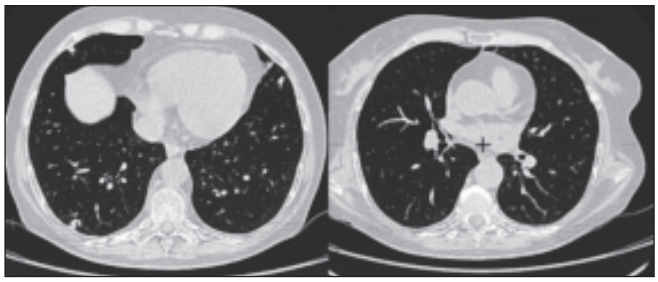

Fig. 3. *Chest CT scan (April 2022). Single small nodes in the lower parts of the lungs*

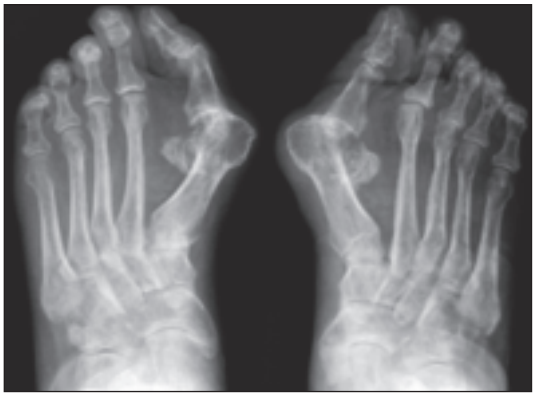

Fig. 5. *Radiographs of the feet (April 2022). Areas of cystic restructuring and erosive changes in the heads of metatarsals III and IV. Subluxation of the third and fourth metatarsophalangeal joints and dislocation of the first metatarsophalangeal joint*

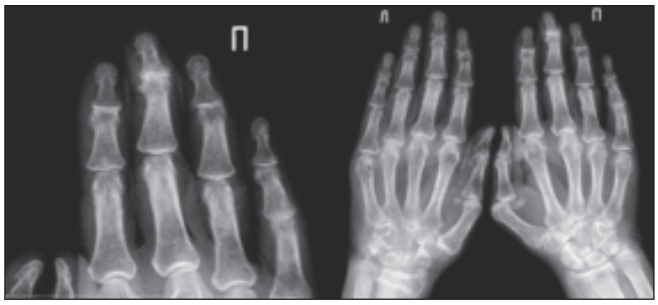

Fig. 4. *X-ray of the hands (April 2022). The joint spaces are narrowed, more prominently on the left side, large erosion of the distal interphalangeal joint of the third finger of the right hand. Areas of cystic lesions in the wrist bones and metacarpal heads*

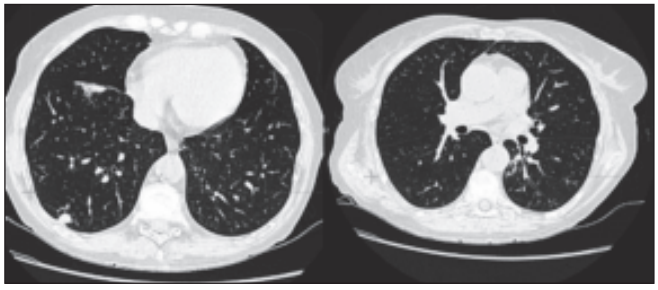

Fig. 6. *Chest CT scan (October 2022). 6 months after the first examination, an enlargement of the nodes is detected*

of the anterolateral segments of the V and VI ribs on the left, the anterior segment of the III rib on the right. Conclusion: multiple focal changes in the lungs, Lung RADS 4B (metastases? pulmonary manifestations of RA?). Area of bronchiolitis in S7 on the right. "Mosaic" pneumatization of the upper parts of the lungs (ventilation, perfusion disorders?). Negative dynamics in the form of a significant increase in the size of previously identified lesions, the appearance of new small lesions in the right lung and a "fresh" area of bronchiolitis in S7 on the right (Fig. 7).

The Diaskintest and Quantiferon test were repeated; a negative result was obtained when examining the sputum for acid-fast mycobacteria. A biopsy of lung tissue was performed (April 2023). Macroscopic description (in a health care facility at the place of residence): a fragment of lung tissue with the presence of a round dense formation with clear boundaries, grayish-yellowish color, homogeneous structure. Microscopic description: in the submitted material, an adequately removed section of lung tissue shows a microscopic picture of a formed old solitary tuberculoma with signs of progression (refreshing) of the inflammatory process, zones of caseous necrosis, unevenly expressed mononuclear cell infiltration, with the presence of giant multinucleated cells. Conclusion: microscopic picture of secondary tuberculosis with the formation of old solitary tuberculoma with signs of progression of the inflammatory process.

At the same time, when performing a polymerase chain reaction, DNA of mycobacteria of the tuberculosis complex was not detected in the same biopsy sample. The patient was re-consulted by a phthisiatrician due to the atypical clinical picture and the absence of signs of infection with mycobacteria according to laboratory tests. Glasses and blocks of biopsy material were sent to an expert institution. The morphological picture is shown in fig. 8, 9.

Expert conclusion: in the lung tissue there is an area of coagulative necrosis, surrounded by fibrous and granulation tissue with focal and diffuse mild lymphoid infiltration. No acid-fast mycobacteria were detected by Ziehl–Neelsen staining. Conclusion: in the studied material there are no signs of specific (tuberculosis) inflammation; productive-necrotic changes in the lung may be caused by RA.

Thus, when studying a lung biopsy, two mutually exclusive conclusions were obtained – both in favor of tuberculosis and against it. However, the absence of DNA of tuberculous mycobacterium in the biopsy specimen, negative results of sputum analysis and Diaskintest, as well as uncharacteristic changes according to the chest CT data and the conclusion of a phthisiatrician about the absence of a tuberculosis process, supported by the results of a morphological study of a lung biopsy specimen in an expert-level institution, allowed us to reject the assumption of the presence of lung damage caused by an oncological or tuberculosis process. Nodules in the lungs were regarded as a systemic manifestation of RA. In January 2023, MT was canceled due to the absence of inflammatory changes in the joints.

In April 2023, CT of the chest was repeated (the fourth study). Multiple focal formations were identified in both lungs, concentrated more in the lower sections and more on the right, a few of them with air cavities. Condition after resection of the right lung. Compared to the previous study from October 2022, multidirectional dynamics were noted: individual foci increased (up to +6.0 mm), decay cavities

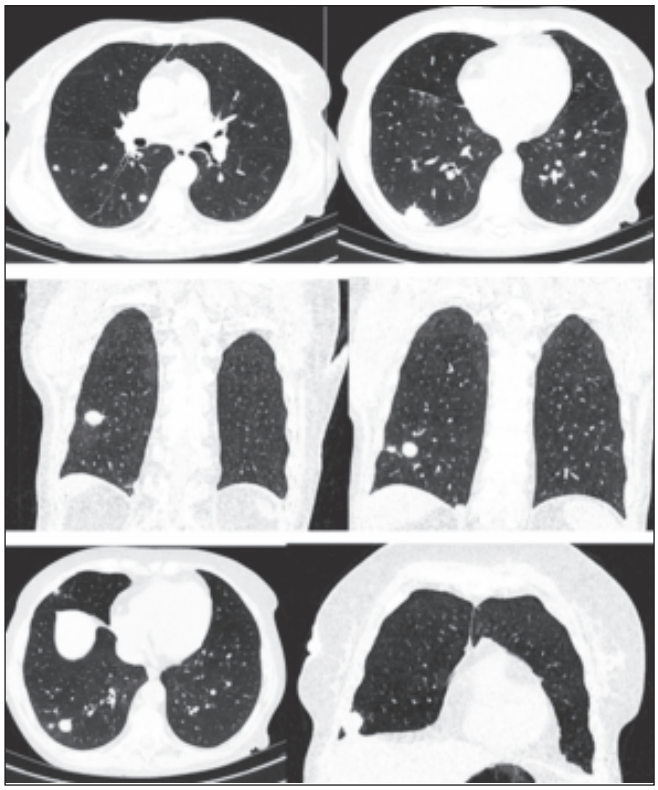

Fig. 7. *Chest CT scan (April 2023), the third scan before a lung biopsy*

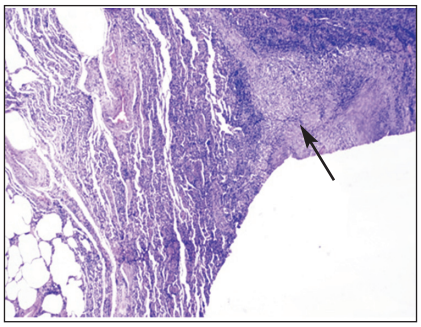

Fig. 8. *Pulmonary parenchyma. Rheumatoid nodule (arrow), focus of fibrinoid necrosis, palisade-shaped histiocytes and lymphocytes at the periphery. Hematoxylin and eosin staining. Magnification ×50*

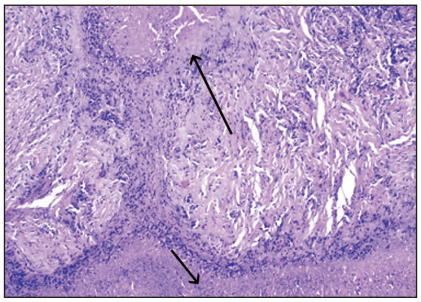

Fig. 9. *Rheumatoid nodules in the lung tissue (arrows), foci with "geographic" fibrinoid necrosis, histiocytes and lymphocytes at the periphery. Hematoxylin and eosin staining. Magnification ×100*

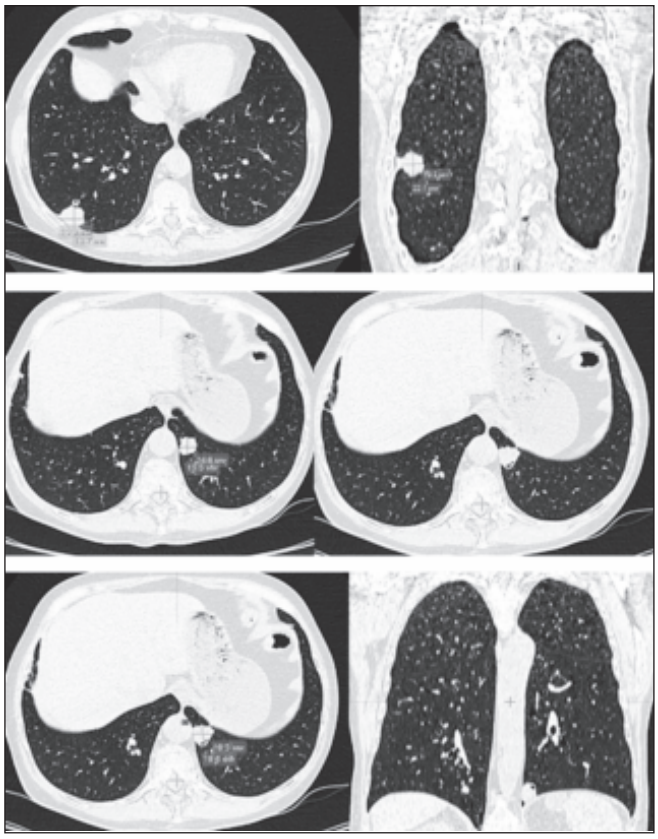

Fig. 10. *Chest CT scan (April 2023), fourth examination. Several small solid foci and focal lesions ranging in size from 1.5 to 23×17×23 mm are detected in both lungs (the largest foci are located in S10 of the right lung along the costal pleura). The lesions are more concentrated in the lower parts of the lungs and more on the right side. A single focal lesion in the peripheral parts in S10 on the left with a diameter of 20×19×21 mm has two elongated air cavities of 3.9×1.7 and 3.1×1.4 mm. In S6 of the right lung there is a 6.9 mm lesion with an air cavity with a diameter of 2.1 mm. In S4 of the middle lobe of the right lung, a metal suture is visible along the costal and lower part of the oblique interlobar pleura against a background of fibrous changes (condition after resection)*

appeared, and the phenomena of bronchiolitis in S7 on the right regressed (Fig. 10).

The patient's condition remained stable, complete clinical remission was observed in the form of normalization of ESR, CRP level, absence of painful and swollen joints. There were no complaints from the respiratory tract.

Since no objective data indicating a tuberculosis or oncological process was obtained, a decision was made to continue RTM therapy. At the same time, the MT was cancelled. Against the background of RTM monotherapy, the picture in the lungs stabilized; no negative dynamics were detected on CT of the chest in July 2023 (Fig. 11): rheumatoid nodes were visualized in S10 on the left (26×16.5×18.5 mm) and in S6 on the right (22×17×16.5 mm) homogeneous structure without cavities, without dynamics.

In December 2023, stabilization of the pulmonary process remained, no growth of rheumatoid nodes was recorded.

Discussion. The presented data emphasize the complexity of the problem of differential diagnosis of lung damage in rheumatic

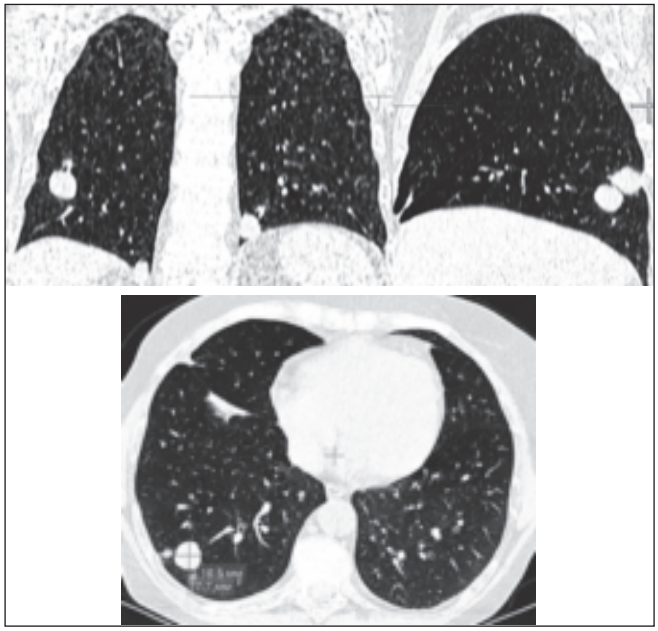

Fig. 11. *Chest CT scan (July 2023), fifth study*

diseases, in particular in RA, covering a wide range of disciplines of clinical medicine. In the above observation, attention is drawn to the progression of pulmonary formations during the combination therapy of MT and RTM, which stopped after discontinuation of MT, which gives grounds to discuss the connection between the development of rheumatoid nodes of the pulmonary localization and treatment with this drug.

Alertness regarding lung lesions (CT chest scan was performed once every 6 months and then every 3 months) made it possible to timely detect an increase in the size of the lesions, perform a lung biopsy as soon as possible and, with a morphological study, exclude other causes of solid formations in the lungs, confirming the presence of a rheumatoid node, cancel MT and achieve stabilization of the process without discontinuation of RTM and without clinical deterioration.

The uniqueness of our observation lies in the negative dynamics, which manifested itself precisely in the growth of intrapulmonary lesions during MTX therapy, while, according to the literature, the most common complications of such therapy are infections and pneumonitis [10]. The range of typical imaging findings and treatment-related complications is very diverse [11]. Our observation resembles that described by A. Balbir-Gurman et al. [12] – a case of development of pulmonary nodules with sterile pleural effusion during MTX therapy in a patient with psoriatic arthritis. Interestingly, in the mentioned case, pulmonary nodules were detected one year after the start of MTX therapy, when a chest CT scan was first performed due to dyspnea. Canceling MT, as in our patient, led to stabilization of the process and cessation of the progression of pulmonary formations. However, the delay in performing a CT scan of the chest (the study was carried out only after the onset of shortness of breath) resulted in late discontinuation of MT and the development of complications of therapy.

Conclusion. Our observation allows us to discuss the possibility of RTM monotherapy in elderly patients with lung damage in order to reduce their risk of infectious and other adverse reactions. It can also be noted that even the use of the "gold standard" of diagnosis – a lung biopsy – does not always make it possible to unambiguously determine the genesis of formations and sometimes a re-examination of the slides at an expert level or a re-biopsy is required. Apparently, we can also discuss the different (depending on the clinical situation) frequency of performing chest CT in patients with rheumatic diseases who have lung damage as part of the underlying disease.

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Conflict of Interest Statement

The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

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