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НЕОБРАТИМЫЕ ИЗМЕНЕНИЯ ЛЁГКИХ В ИСХОДЕ ПОВРЕЖДЕНИЯ ПРИ COVID-19 — РАЗМЫШЛЕНИЯ НА ТЕМУ И ПРИМЕРЫ ЛУЧЕВЫХ ИЗОБРАЖЕНИЙ

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Irreversible Lung Transformation Resulting from Damage In COVID-19 — Discourses and Examples of CT Images

Резюме

Проблема формирования необратимых остаточных изменений после перенесенного вирусного повреждения легких при COVID-19 (COronaVIrus Disease 2019, новая коронавирусная инфекция) по прошествии двух лет пандемии остается важной и обсуждаемой. Это связано с большим числом пациентов, перенесших коронавирусную инфекцию (в т.ч. со значимым объемом поражения легких) и возможным неблагоприятным прогнозом с уменьшением качества и продолжительности жизни. С учетом того, что в последнее время активно применяется антифибротическая терапия ряда интерстициальных заболеваний легких (при идиопатическом легочном фиброзе и системных заболеваниях), рассматривается вопрос о возможном использовании этих средств и при неблагоприятном исходе COVID-19. Однако до сих пор точно неизвестно, насколько часто развивается фиброз в исходе новой коронавирусной инфекции, а также четко не выделены группы пациентов, которые могут иметь неблагоприятный прогноз в виде исхода в фиброз.

В обзоре рассмотрены патогенетические аспекты возможного развития необратимых изменений у пациентов с COVID-19, предрасполагающие факторы, а также особенности диагностики с акцентом на КТ-визуализацию с собственными наблюдениями авторов.

Ключевые слова: *коронавирус, COVID-19, фиброз, интерстициальное заболевание легких, компьютерная томография, бронхоэктазы, «матовое стекло»*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The problem of the formation of irreversible residual changes after suffering viral lung damage with COVID-19 (COronaVIrus Disease 2019) after two years of the pandemic remains important and discussed. This is due to a large number of patients who have had a coronavirus infection (including those with a large amount of lung damage) and a possible unfavorable prognosis with a decrease in the quality and life expectancy. Given the fact that antifibrotic therapy has recently been actively used for a number of interstitial lung diseases (with idiopathic pulmonary fibrosis and systemic diseases), the question of the possible use of these drugs in case of an unfavorable outcome of COVID-19 is being considered. However, it is still not known exactly how often fibrosis develops in the outcome of a new coronavirus infection, and groups of patients who may have a poor prognosis in the form of an outcome in fibrosis have not been clearly identified.

The review considers the pathogenetic aspects of the possible development of irreversible changes in patients with COVID-19, predisposing factors, as well as diagnostic features with an emphasis on CT scan with the authors' own observations.

Key words: *coronavirus, COVID-19, fibrosis, interstitial lung disease, CT scan, bronchiectasis, ground glass opacities*

Conflict of interests

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ACE — angiotensin-converting enzyme, ARDS — acute respiratory distress syndrome, AV — artificial ventilation, COPD — chronic obstructive pulmonary disease, CT — computed tomography, DAD — diffuse alveolar damage, DLCO — diffusing capacity of the lungs, ECMO — extracorporeal membrane oxygenation, GCs — glucocorticoids, ILD — interstitial lung disease, OP — organizing pneumonia, PF — pulmonary fibrosis, RF — respiratory function, SARS — severe acute respiratory syndrome

Lung lesion during the acute phase of COVID-19 (COronaVIrus Disease 2019, a novel coronavirus infection) is not a specific condition. SARS-COV-2 virus in lung tissue causes the development of diffuse alveolar damage (DAD) in combination with the signs of vasculitis [1]; their stage and prevalence correlate with the clinical presentation. The same changes are observed in patients with acute respiratory distress syndrome (ARDS), as well as with diseases caused by other viruses — the most illustrative example of them is H1N1 flu. Due to the fact that DAD develops through typical phases (exudative, proliferative), its possible outcome is the pulmonary fibrosis (PF) that is observed in patients after ARDS and is registered in patients as the outcome of severe influenza. For example, in ARDS, not associated with a virus, PF is detected during autopsy in 4 % after one week of ARDS manifestations, in 24 % — between week 1 and week 3, and in 61 % after 3 weeks [2]. Therefore, PF can also develop in patients with COVID-19. However, not all patients with coronavirus infection develop clinical signs of ARDS which is significant for prognostic evaluation. Based on literature, SARS-COV2-associated ARDS is diagnosed in 5-40 % of cases [3, 4], and it is this particular group of patients that can potentially have a negative prognosis in terms of development of an irreversible process. To compare, PF development in patients with SARS (Severe Acute Respiratory Syndrome) was observed in up to 8 % of cases, in those with H7N9 influenza — in up to 20 % [5].

Notably that the definitions regarding long-term changes in lungs after coronavirus infection are quite diverse. Alongside with the term “fibrosis”, the literature sources contain the references to post-COVID interstitial lung disease (ILD), organizing pneumonia (OP), and fibrotic lesions [6, 7]. Generally, it seems to be a more correct approach, since not every type of post-COVID ILD innevitably results in PF. According to Aronson K.I. et al., the true prevalence, as well as the feasibility of management of these conditions with glucocorticoids (GCs) should be established in large studies; besides, the computed tomography (CT) findings should be confirmed by morphological studies [8].

The prevalence of post-COVID PF is predicted to constitute 10-15 cases per 10,000 people which is ten times as high as the risk of idiopathic pulmonary fibrosis development [7]. However, we can hardly say that this phenomenon is widespread in current pandemic. Neither pulmonologists nor radiologists observe a high incidence of fibrosis as an outcome of pulmonary lesions in their practice. This fact may be attributed both to certain SARS-COV-2 features and to the changes in the therapeutic approach — the use of biological agents (IL-6 inhibitors) to stop the excessive immune response, widespread use of GCs in both acute and delayed periods of infection. All these facts may result in lower severity of nonspecific inflammation in lung tissue and is the prevention of fibrotic process, and promotes positive changes in OP with no gross structural changes.

It was found that the SARS-COV-2 virus itself, when combined with an angiotensin-converting enzyme (ACE), increases angiotensin II level to activate the connective tissue growth factor (CTGF), involved in the development of fibrosis [9]. In the review by Ademola S. Ojo et al. (2020), the pathogenesis of PF as the outcome of a severe or long-term process is associated with the damage to the basement membrane of cells and the transformation of sites of organization into fixed or progressive tissue with fibroblasts with further impairment of lung architecture [10].

In the early days of this novel coronavirus infection, physicians often had erroneous opinion about the development of PF in patients that was based on the analysis of CT results in 2-3 weeks after the acute period and one dynamic CT examination; it is definitely not a reliable conclusion. The intermediate changes that from morphological viewpoint are the areas of organization and atelectasis of various lengths (both lobular and typical discoid) were misdiagnosed as PF; on CT images, they are visualized as linear and radial consolidation strips with clear contours (Figure 1).

The frequent development of reversible atelectases may be associated with the viral damage of type II alveolar cells (in the course of DAD) that produce a surfactant [11]. Subsequently, it was observed that such atelectases were completely resolved [12] which is most likely due to the gradual regeneration of type II alveolar cells and improved microcirculation. We can also assume the presence of the impairments of pulmonary ventilation associated with a musculoskeletal system imbalance, i.e. the weakness of intercostal muscles, diaphragm, their impaired innervation, etc. Theoretically, all these factors can result in the development of atelectases. It should be taken into consideration that lung tissue can stay collapsed for a relatively long time with no structural changes (up to two months) [11]. Later, an irreversible process of interstitial structures, bronchi and vessels deformation will develop in this atelectasized area, and PF-equivalent changes will be observed. The complete resolution of post-COVID-19 changes in lungs is observed 6 months after hospitalization in 50 % of patients, and 9 months — in 75 % [13].

The comprehensive monitoring of PF-suspected patients as the outcome of COVID-19 remains an important issue. First of all, one should assess the persistence of clinical signs or their aggravation. Special attention should be paid to long-term dyspnea or its aggravation after the acute stage of viral process, weakness and tachycardia [14], as well as the possible oxygen dependence. The useful functional methods include respiratory function (RF) tests and the measurement of diffusing capacity of the lungs (DLCO). For example, according to Zaitsev A.A. et al. (2020), 3 weeks after discharge from the hospital, dyspnea persists in 50 % of patients, restrictive impairments of respiratory function are detected in 15.6 %, and DCL of different grades decreases in 56 % of cases. The authors observed the greatest decrease in DCL in patients with massive persistent changes on CT [15]. Qin W. et al. (2021) also mentioned a correlation between the presence of traction bronchiectases, reticular changes and subpleural thickening with decreased DCL parameters [14].

It is reasonable to identify clinical and radiological groups that later may be prone to PF. As a rule, in patients with small and medium lung lesions (up to 50 %), the changes gradually resolve completely, except for the residual areas of ground-glass opacity with no reticular striation that can persist for quite a long time and are not reliable indicators of fibrosis onset. Special attention should be paid to the patients with a severe clinical course of the disease and large lung damage (more than 50 %) who stayed in hospital for a long time and/or were treated in intensive care units (the highest correlation with a decrease in DCL parameters is observed in connection with artificial ventilation) [9,16,17]. Smoking and previous alcohol consumption (as additional factors of respiratory symptoms aggravation), age (a tendency to fibrosis development with age) are also distinguished as risk factors [18]. The patients with a "frozen" ground glass pattern, despite ongoing therapy, should subject to follow-up for PF development; this sign may indicate

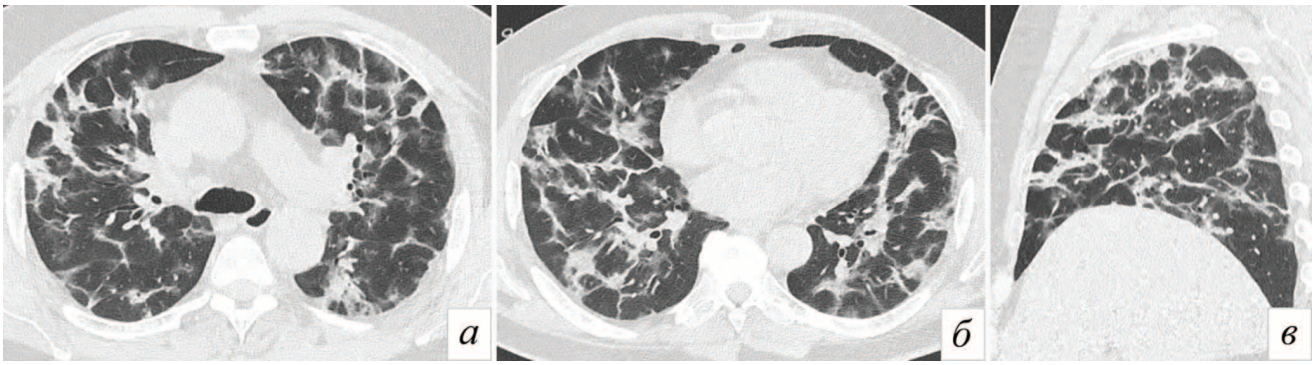

Figure 1. *Patient K, 55 years old. The early resolution phase of lung injury in COVID-19. Thoracic CT scans in axial (а, б) and sagittal (в) projections. Multiple band-like strips of consolidation, perilobular hardenings. This CT picture is presented by the pattern of OP in combination with discoid atelectasis, which can be mistaken for fibrotic changes*

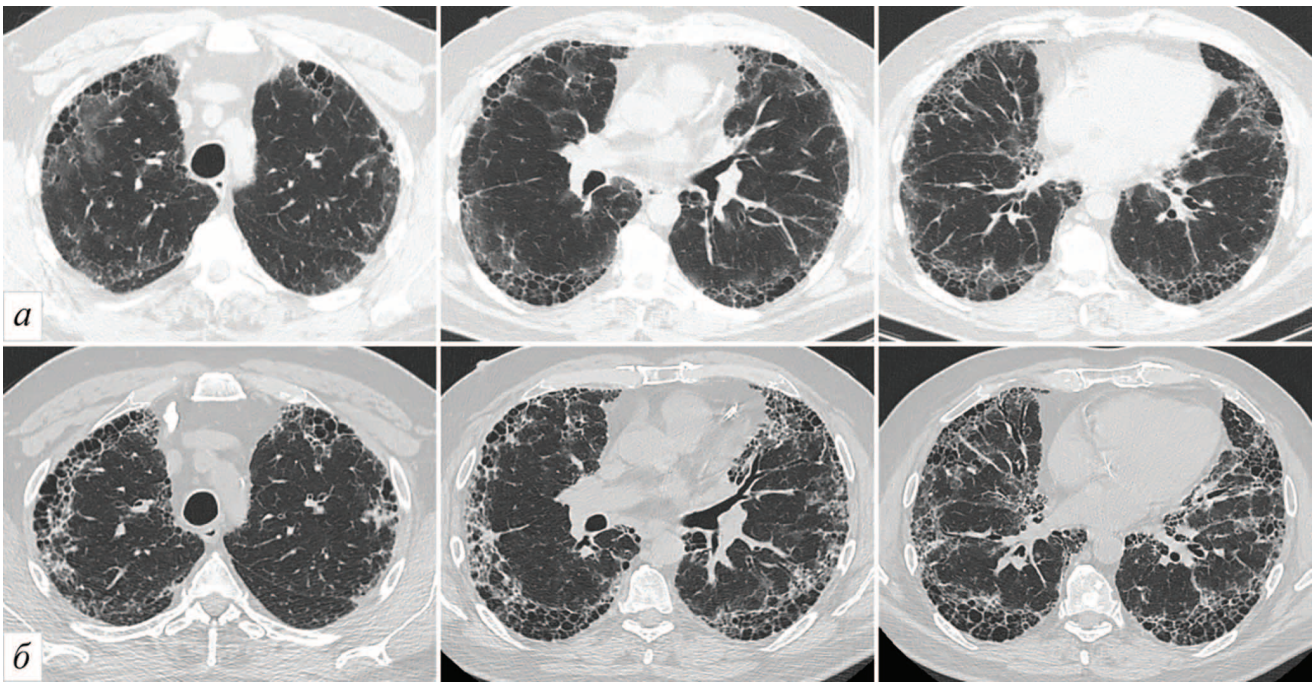

Figure 2. *Patient N., 58 years old. COVID-19 (PCR+) on the background of usual interstitial pneumonia. Axial chest CT scans at appropriate levels. Row A — the study dated 07.03 2021, row Б — the study dated 21.04.2021. In dynamics, in place of areas of "ground glass" the appearance of pronounced reticular changes and structural realignment in the form of a "honeycomb lung", the progression of "honeycombs" in the already existing areas, the appearance of their additional rows*

a persistent morphological DAD pattern in lungs. The pre-existing premorbid background represented by a fibrous process associated with various ILDs or systemic diseases can contribute to the progression of fibrosis in previously intact areas in the presence of viral damage; otherwise, it can change the CT presentation (for example, the development of a "honeycomb lung" associated with the pre-existing isolated reticular changes) (Fig. 2). One can find the examples of such transformations in the papers of Speranskaya A.A. et. al. [19]. With an extensive CT pattern of OP at the end of acute phase, one can expect a gradual development of PF with no adequate GCs treatment. It is these groups of patients that will require special pulmonologist's attention during the follow-up, including regular CT examinations — in 3-6-12 months, etc., if necessary.

Radiation diagnostics

CT is helpful for assessment of the possible development of irreversible changes due to its high sensitivity, especially when it comes to small pathological areas localized in the basal sections of lungs. Conventional X-ray is globally used as a primary diagnostic method, however, for long-term structural consequences, CT is the method of choice [17].

Visualization of changes in lungs is crucial for registration the signs of PF or its equivalents. It is related to the fact that a morphological study is not quite common in such cases and can worsen the current pulmonary symptoms, resulting in complications (pneumothorax, bleeding) associated with the compromised lung tissue at the stage of convalescence after the damage. Considering the development of the "post-COVID" syndrome, clinical presentation can also persist for quite a long time, or even aggravate for reasons that are not related to lung damage (one of the important mechanisms is extensive vasculitis, coagulopathy) [1]. Therefore, it is visualization that will allow identifying definite criteria for the development of a fibrotic process in patients and to objectify them.

The most important factor for a radiologist's conclusion will be the monitoring the changes over time: the continuance of visualization of the changes identified or their progression. The results of one isolated CT examination, or the results obtained shortly after the acute stage are not relevant to make a conclusion on PF. In other diseases (for example, tuberculosis), morphologists have previously highlighted the resolution of several seemingly irreversible changes. Strukov A. I. indicates that such reverse development of atelectases, retention bronchiectases and carnification areas (which are actually OP) is admissible [20]. For example, the decreased diameter of bronchial lumen over time with no structural changes of the wall, in case of resolution of the adjacent infiltration, illustrates the reversibility of the process rather than the development of true bronchiectasis. The dilatation of bronchial lumen, especially in the lower lobes, is often observed in patients with viral lung damage at the stage of resolution and even in the acute

phase; it is associated with de-airing and infiltration of lung tissue that results in temporary decrease of its volume. The same is true for the functional lung tests — the importance of follow-up over time and comparison with previous results. It is also important to observe the typical changes associated with the previous areas of ground-glass opacity/consolidations over time [17].

When can a radiologist suspect irreversible changes in lungs as the outcome of COVID-19 according to CT results? Based on our own clinical experience, the most significant signs are as follows:

- the decreased volume of the anatomical region of lung (segment, lobe) which is especially distinctive by the location of the of interlobar pleura layers. One can also pay attention to the overall decrease in lung volume associated with the normal depth of inhale (Fig. 3). When visualizing such changes, one should exclude other causes of the volume decrease associated with bronchial patency, that is, bronchial tumors, mucopurulent and hemorrhagic clots, secondary destructive processes, etc.
- Deformation and dilatation of the lumen of bronchi/bronchioles with the development of traction broncho/bronchiolectasis (Fig. 3e, Fig. 4). Alongside with the deformation, one can also observe the convergence of bronchovascular bundles in the affected lung part. According to Huang W. et al. (2021), dilated bronchial lumen, as a manifestation of PF, is the most common sign — it is presented in up to 80 % of cases [21]. If this is the case, one should evaluate the results of all previous x-ray examinations, since bronchial dilatation could have developed in a patient long before the viral infection, among others, due to the chronic obstructive disease (COPD) which is often characterized by cylindrical bronchiectasis. It should be remembered that the bronchial lumen dilatation in the areas of OP can be potentially reversible after the intraalveolar granulations reduction. Radiologist should be especially careful in the interpretation of such detected changes. The changes in the shape of the bronchi represented by varicose bronchiectases and bronchioectases with typical wave-shaped wall are more suspicious of an irreversible process.
- Intrapulmonary and pleural-pulmonary strands that persist over time and are often located in the area of deformed bronchi and surround them. The large amount of such strands spreading in different directions can produce an impression of background ground-glass opacity that indicates either a certain averaging of the surrounding density, or fine-structure fibrosis (Figure 5).

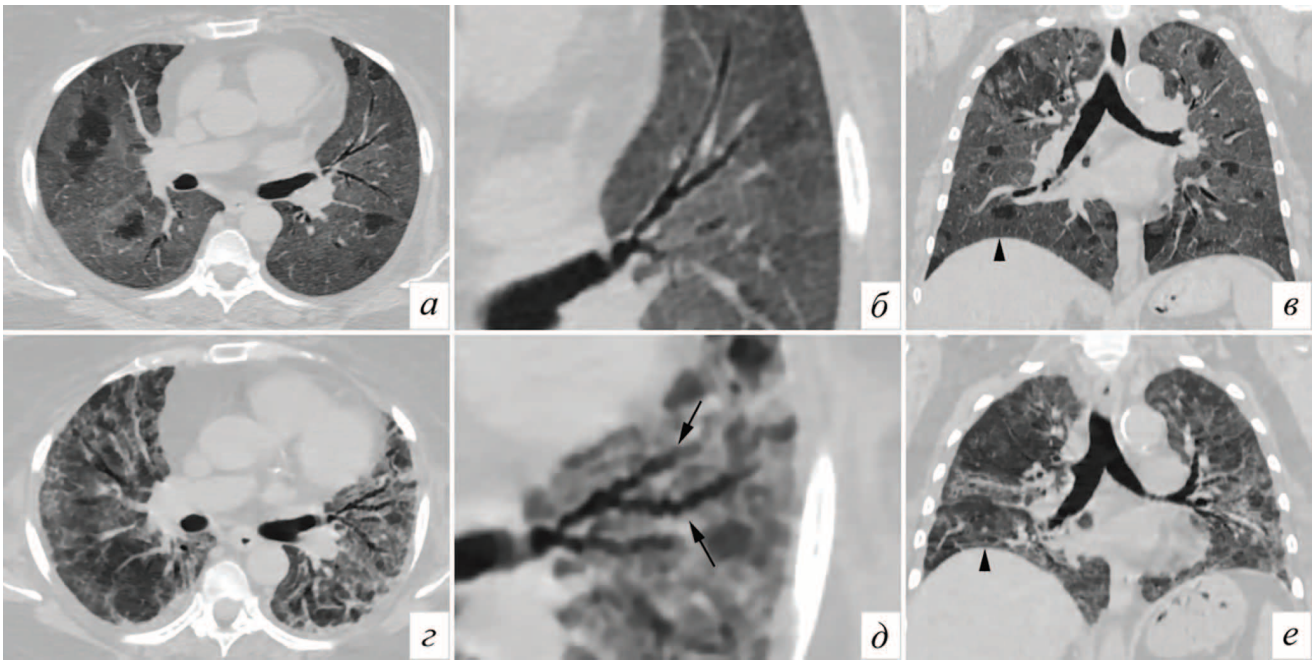

Figure 3. *Patient F., 60 years old. COVID-19 (PCR+). Thoracic CT scans in axial projection (а, г), coronal projection (в, е) and enlarged fragments (б, д) at appropriate levels. The upper row — the study dated 23.11.2020, the lower row — the study dated 25.12.2020. Against the background of heterogeneous hardenings in both lungs, the appearance of traction (varicose) bronchiectase in the upper lobe on the left (arrows) are clearly visible, which were absent before. In other parts of the lungs there is no such deformation. Also, in the dynamics there is a general decrease in lung volume at the same depth of inspiration (в, е), a high position of the dome of the diaphragm (arrowheads). The changes may be potentially reversible*

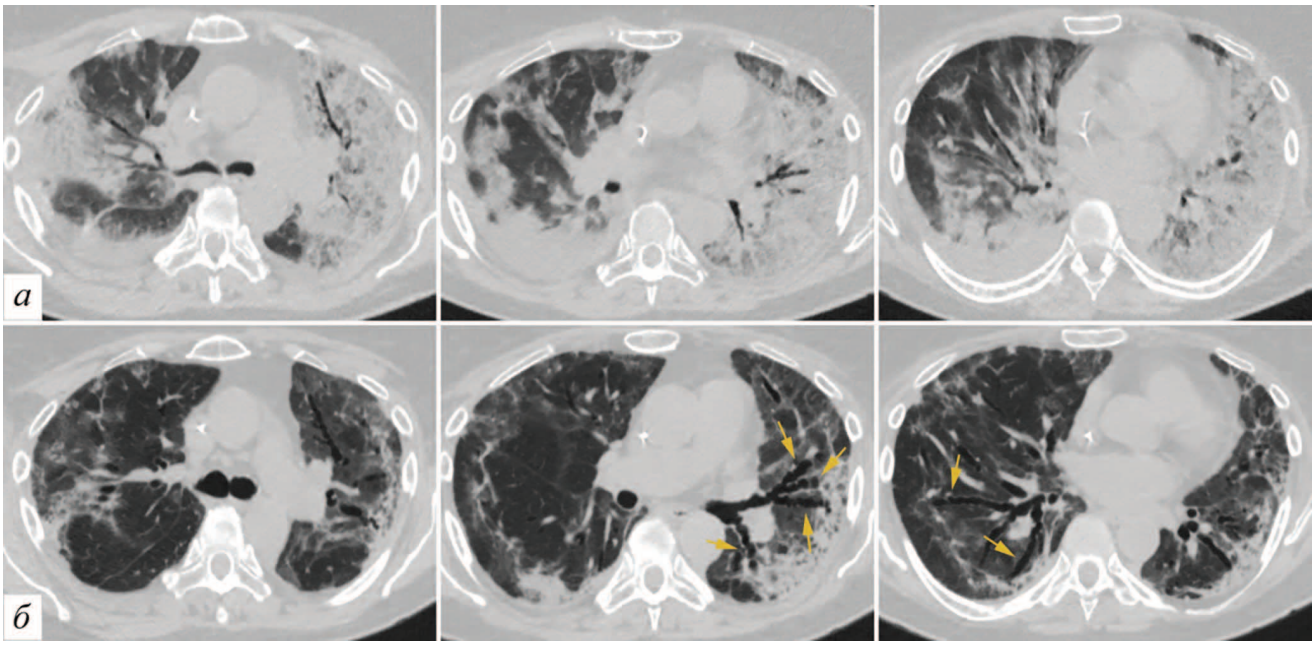

Figure 4. *Patient A., 74 years old. COVID-19 (PCR+). Thoracic CT scans in the axial projection. Row a — study dated 03/25/2021 and row b — study dated 04/19/2021 at the corresponding levels, taking into account different depths of inspiration. Top (a) — CT picture of acute viral damage with a lesion volume of at least 75 %. Below (b) — dynamics at the stage of resolution, the appearance of deformation and expansion of the lumens of large bronchi, especially in the lower parts of the lungs (arrows)*

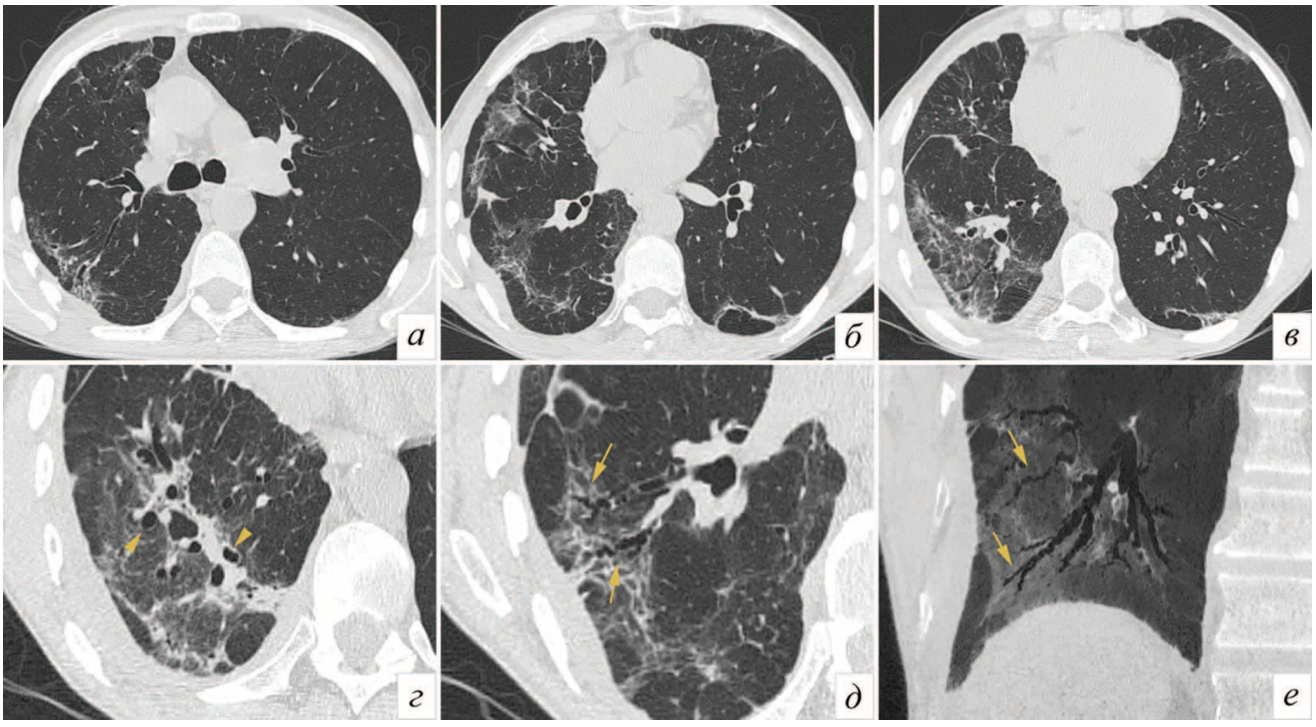

Figure 5. *Patient K., 73 years old. 4 weeks after discharge for COVID-19 (PCR+). Thoracic CT scans in the axial projection (a-в), enlarged image fragments (г, д) and MinIP reformation (е). Against the background of low-intensity areas of "ground glass" (more on the right), there are stringy hardenings that deform the lung tissue and pleura. Cylindrical (arrow heads) and varicose (arrows) broncho- and bronchiolectasis are also visualized*

- The persistent areas of consolidation and ground-glass opacity with reticular changes that indicate the interstitium involvement in the pathological process [6] (inter alia, due to the decreased volume of the lobe). These areas are deaerated fragments of lung replaced by connective tissue (of varying severity). They can have homogeneous structure or include bronchiectases. Unlike reversible atelectasized tissue, these areas do not accumulate contrast agent. In the presence of one such subpleural area, one should also think about past lung infarction that can also turn into a fibrosis area.
- Thickening of pleura that is more often observed along the costal sheets. This symptom is often associated with the contracture of lung tissue (and therefore, vessels and bronchi) and subpleural strands.
- Pneumatocele is the areas of the impaired architecture of lung tissue with the development of air pseudocavities that are mainly found in the peripheral parts of lungs [17]. Alarcon-Rodrigues J. et al. (2021) give an example when pneumatoceles are partially reversible [17]. However, pneumatocele as the only sign can be hardly defined as a strict criterion of fibrosis. We recommend to consider a comprehensive assessment, for example, pneumatocele associated with ground-glass opacity, consolidations, or in the area of deformed bronchi as additional signs. We have also observed the closure of such lesions over time.
- In the most severe cases, there is a gross deformation of secondary pulmonary lobules with the development of the subpleural areas of honeycomb lung — in up to 7 % of cases [21] (Figure 6). In our practice, we mainly observed the progression of honeycomb in the place of viral damage in patients with a pre-existing presentation of PF, for example, as a common interstitial pneumonia rather, than its development in previously intact areas. At the same time, the deterioration of CT results can develop as early as in 1-2 months after the acute process.
- The long-term persistence of the abovementioned common changes in lungs can result in dilated right heart, as well as dilated and lengthened pulmonary artery trunk.
- Other possible changes, like air-trapping, are also described [21].

The areas of ground-glass opacity in the long-term follow-up period with no reticular changes call for careful interpretation in relation to PF. We observed such changes in a female patient with no current respiratory complaints one year after the acute period of the disease (Figure 7). The observations made in our clinic are compliant with the opinion of Samsonova M.V. et al. (2021) who suggest long-term persistence of ground-glass opacity in lungs on CT due to nonspecific interstitial pneumonia, or isolated intraalveolar edema, potentially in combination with hemorrhages or OP [22]. The air-trapping areas can be actually represented by a mosaic pattern associated with thrombosis of the branches of

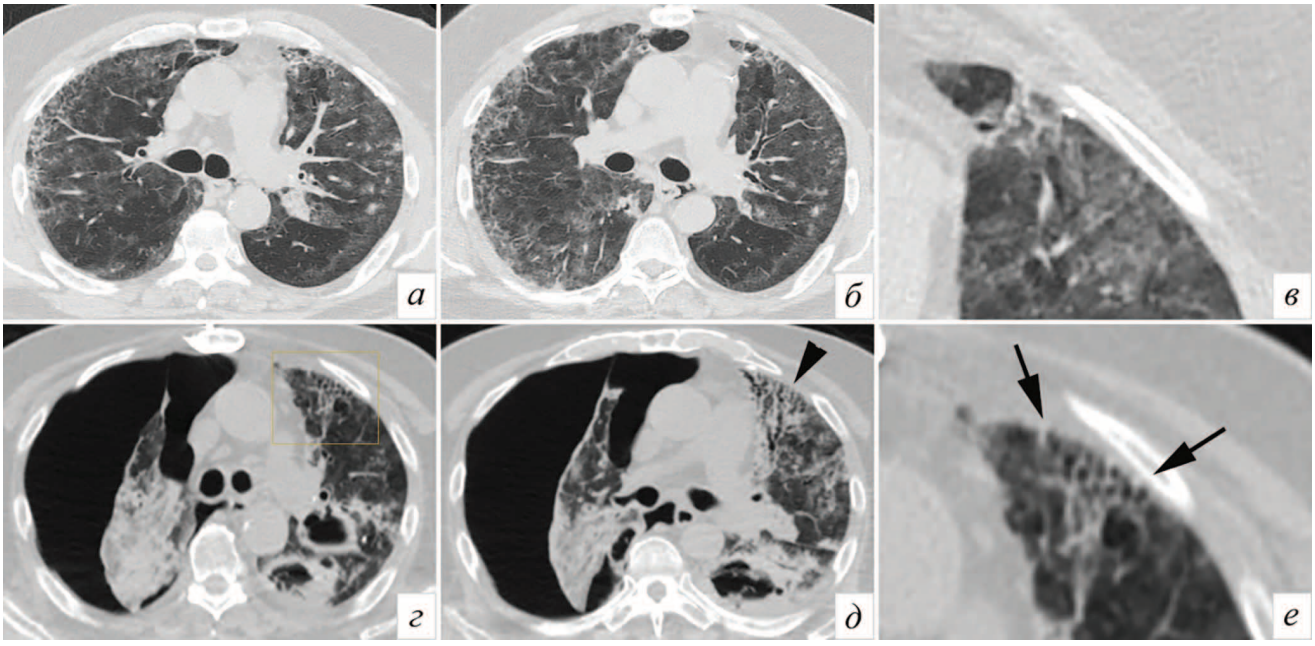

Figure 6. *Patient M., 65 years old. COVID-19 (PCR+). Thoracic CT scans in the axial projection (a-e) with enlarged fragments (в, e) at the corresponding levels. The top row — the study dated 08/04/2021, the bottom row — the study dated 09/16/2021. Secondary infection (cavities) and pneumothorax on the right, in S3 on the left there is an area with varicose broncho- and bronchiolectasia (arrow head), as well as an area similar to a "honeycomb" deformation (frame, arrows)*

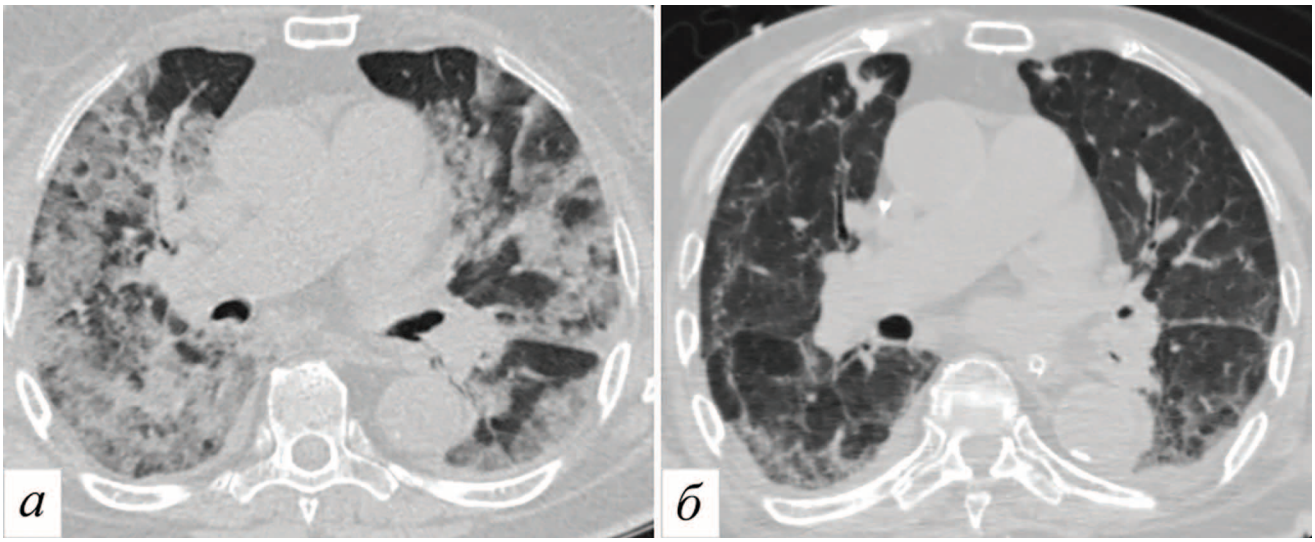

Figure 7. *Patient A., 88 years old. COVID-19 (PCR+), one year after the acute phase of the disease. Thoracic CT scans in the axial projection, a — examination dated November 4, 2020, б — examination dated November 2, 2021. In place of extensive hardenings (consolidations, "ground glass"), there remain inhomogeneous areas of "ground glass" of low intensity with fuzzy contours, against which linear hardenings are presented, incl. in the form of characteristic arcs. Bronchiectasia and other areas of deformity are not clearly visible, and changes may correspond to OP or a pattern of nonspecific interstitial pneumonia*

pulmonary artery due to hypercoagulation [22] and, as a consequence, redistribution of pulmonary blood flow that creates this typical mosaic pattern. The results obtained by Jia-Ni Zou et al. (2022) indicate the incidence of fibrosis in 90 days after COVID-19 in 84.15 % of cases, mainly due to the persistent areas of ground-glass opacity (from 80.7 to 96.5 %), linear thickenings and reticular changes [23]. Such high numbers should be interpreted carefully due to too early follow-up period: some of these thickenings and linear structures could have resolved later and would no longer be regarded by the authors as PF. These conclusions are also not confirmed by morphological studies and are based only on CT results.

The most gross changes represented by true PF are observed in the patients who have been on artificial ventilation (AV) for a long time, as well as in those who underwent extracorporeal membrane oxygenation (ECMO) after extensive DAD with a lung lesion approximating 100 % and the inevitable development of a secondary bacterial infection. As a rule, when a patient stays in an intensive care unit with artificial respiratory support for 1-2 months, they develop a common deformity in the form of a honeycomb lung and bronchiectases. In most cases, lung transplantation should be considered for such patients [24].

An important task for radiologist is to determine how extensive the above-described symptoms are and to register them in the records. It should be understood that the presence of only a single area that is typical of PF is likely to have no high clinical significance due to the compensatory capabilities of lung tissue. The extensive changes on both sides, with decreased lung volume and significantly impaired architecture will be considered significant. Assumptions are made about the need to determine the volume of fibrotic lung damage similarly to the assessment in the acute COVID-19 period (CT-1, CT-2, etc.); and it will be relevant not only for this disease but for other fibrotic processes in lungs as well (for example, J.H Warrick, A.U. Wells scores, etc.) [25].

The detection of PF signs by a radiologist should not be the only cause for a pulmonologist's decision on further routing and administration of special treatment. CT data demonstrate only a pattern that naturally corresponds to irreversible changes, and their clinical significance should be determined together with clinical and instrumental examinations and functional tests. A similar situation is observed in the patients with COPD. The results of radiological examinations can help to determine emphysema, chronic bronchitis, bronchiectasis, but the diagnosis is made on the basis of functional tests of the patient. This is due to the fact that not only fibrotic changes can contribute to the development of persistent respiratory failure in the patient; it's causative factors can be the extensive microangiopathy that results in thrombosis in situ and the impaired lung perfusion; it can be detected using scintigraphy [26], or iodine maps during contrast-enhanced CT.

Conclusion

The conclusion on irreversible changes in the lungs as the outcome of coronavirus damage is a serious prognostic marker; it should be performed jointly by a multidisciplinary commission in the presence of a pulmonologist, radiologist, functional diagnostics specialist, if possible, ~~and~~ a morphologist. Only if the patient has persistent or progressive clinical signs of respiratory failure in combination with oxygen dependence, decreased parameters or the absence of positive changes during functional tests, and a persistent radiation pattern that is typical for PF, one can conclude on the development of an irreversible process in lungs and decide on the further approach to the treatment of the patient: up to antifibrotic therapy or lung transplantation. At present, based on practical observations, it would be incorrectly to say that irreversible changes in lungs after COVID-19 are a common situation. Radiologists should be especially careful when mentioning the pulmonary fibrosis in their conclusions, since many visible changes can be potentially reversible.

Вклад авторов

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