

Features of pathological anatomy of lungs at COVID-19

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Abstract

The research aim is to study the morphological features of COVID-19 in the lungs of patients who died in Moscow from March 20 to June 6, 2020. **Methods.** Autopsy material of the lungs from 123 deceased (54 women, 69 men) with COVID-19 coronavirus infection (confirmed by PCR) was analyzed, the median age was 71 (30 – 94) years, and the duration of the disease was 14 (3 – 65) days. In all cases, the patient's medical records and autopsy reports were analyzed. Macro- and microscopic changes in the lungs were evaluated in all the observations. **Results.** The pathology of the lungs in COVID-19 corresponds to various phases of diffuse alveolar damage (DAD). The exudative phase of DAD was detected in 54 (43.9%), the proliferative phase – in 21 (14.63%), and their combination – in 51 (41.46%) of the deceased. Histological features of different phases of DAD are described. **Conclusion.** An analysis of autopsy material revealed a mismatch between the duration of the course of the disease and the phase of diffuse alveolar damage. A significant portion of the dead found a combination of exudative and proliferative phases of the disease. Histological signs that indirectly indicate a violation of the coagulation system during COVID-19 are described.

Key words: COVID-19, viral interstitial pneumonia, pathology, coagulopathy.

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Особенности патологической анатомии легких при COVID-19

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Резюме

Целью статьи явилось изучение особенностей морфологических изменений в легких у умерших от COVID-19 в Москве за период 20.03.20–06.06.20. **Материалы и методы.** Проанализирован аутопсийный материал легких умерших от коронавирусной инфекции COVID-19 больных ($n = 123$: 54 женщины, 69 мужчин; средний возраст – 71 (30–94) год; продолжительность заболевания – 14 (3–65) суток), подтвержденной методом полимеразной цепной реакции. Проанализированы медицинские карты всех стационарных больных и все протоколы вскрытий. По данным всех наблюдений оценены макро- и микроскопические изменения в легких. **Результаты.** Патоморфологические изменения в легких соответствовали различным фазам диффузного альвеолярного повреждения (ДАП). Экссудативная фаза ДАП выявлена у 54 (43,9 %), пролиферативная – у 21 (14,63 %), их сочетание – у 51 (41,46 %) умершего. Описаны патогистологические особенности изменений в разные фазы заболевания. **Заключение.** При анализе аутопсийного материала установлено несоответствие между продолжительностью течения заболевания и фазой ДАП. У значительной части умерших обнаружено сочетание экссудативной и пролиферативной фазы заболевания. Описаны гистологические признаки, косвенно указывающие на нарушение системы коагуляции в течении COVID-19.

Ключевые слова: COVID-19, вирусная интерстициальная пневмония, патологическая анатомия, коагулопатия.

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Information about the epidemiology, clinical features, prevention, and treatment of the new coronavirus infection COVID-19 is still limited and is updated almost daily. In December 2019, an outbreak caused by the new coronavirus began in Wuhan, Hubei Province, China, leading to a pandemic declared by the World Health Organization (WHO) on March 11, 2020 [1]. According to phylogenetic studies, the pathogen was named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and the disease was named CORonaVirus Disease-2019 (COVID-19).

The high infectivity of the coronavirus, the lack of effective antiviral drugs and vaccines, and the potentially large number of asymptomatic patients have made it extremely difficult to prevent the spread of COVID-19. Unfortunately, about 20% of infected patients develop severe disease. On July 2, 2020, the mortality rate from COVID-19 in the world was 4.86%, according to the WHO data [2].

It is known that the most severe clinical manifestation of a new variant of coronavirus infection is viral interstitial pneumonia in the form of diffuse alveolar damage (DAD) (clinically ARDS), less often with the development of thrombohemorrhagic syndrome and septic shock. The respiratory distress syndrome that develops in patients with severe COVID-19 may differ from classic acute respiratory distress syndrome (ARDS). However, patients demonstrated the relatively intact lung mechanics in the presence of severe hypoxemia, characterized by high respiratory compliance and a high shunt fraction. Therefore, the pathology and pathophysiology of COVID-19 may differ

from the known ARDS [3]. Dysregulation of the immune response during COVID-19 is characterized by a pro-inflammatory phase with the development of subsequent immune suppression [4]. Furthermore, it is assumed that microvascular disorders are a fundamental pathogenetic aspect leading to death in the most severe course of the disease [5].

Thus, the pathophysiology of the disease is not well understood. Data on the pathomorphological features of the disease are accumulating, but at the moment the number of such publications is limited.

The purpose of this article is to study the pathological changes in the lungs of those who died from COVID-19 in Moscow for the period from March 20 to June 6, 2020.

Materials and methods

The autopsy material of the lungs from 123 dead people (54 women, 69 men) was analyzed, the median age of the dead was 71 (30 – 94) years. In all observations, the inpatient's medical records and autopsy reports were analyzed. All these people had a new coronavirus infection, COVID-19, confirmed in vivo by Polymerase chain reaction (PCR) of nasopharyngeal smears. The duration of the disease (from the onset of symptoms to death) was 14 (3 – 65) days, the duration of hospitalization was 6 (1 – 65) days. Some of the patients underwent mechanical ventilation, the median duration of which was 4 (1 – 30) days.

Table 1
Basic clinical and laboratory findings
Таблица 1

Основные клинические и лабораторные показатели

Characteristic	Value
Sex, female/male	54/69
• Age*, years	71 (30 – 94)
• COVID-19 diagnosis (RT-PCR – naso-, oropharyngeal smears)**, n (%)	123 (100)
Time from the onset of symptoms to death, days*	14 (3–65)
The duration of hospitalization, days*	6 (1 – 62)
The duration of mechanical ventilation, days*	4 (1 – 30)
Comorbid diseases**, n (%):	
Diabetes mellitus, type II	39 (32,5)
Obesity	19 (15,83)
• Arterial hypertension	61 (49,59)
• Chronic ischemic heart disease	30 (24,39)
• Chronic cerebral ischemia	4 (3,25)
• Myocardial infarct	3 (2,5)
• Leukemia, lymphomas	9 (7,5)
• Malignant tumors	5 (4,16)
• Chronic respiratory diseases	15 (12,5)
• HIV	4 (3,33)
• Kidney transplantation	1 (0,83)
• Lung tuberculosis	1 (0,83)
• Paraproctitis	1 (0,83)
• Laboratory parameters:	
• Total leucocyte count ($\times 10^9/L$)***	11,24 $\pm$ 7,29 (1,4 – 31,4)
Absolute lymphocyte count ($\times 10^9/L$)*	0,6 (0 – 9)
CRP, mg/ml*	170 (15 – 431)

Note: RT-PCR, Polymerase chain reaction in real time; CRP, C-reactive protein; *, median (minimum–maximum) for normal distribution quantitative variables; **, absolute values (%); ***, mean values $\pm$ standard deviation (minimum/maximum); reference values: for total number of leukocytes – $(4.0 - 11.0) \times 10^9/l$, for absolute number of lymphocytes – $(1.5 - 4.5) \times 10^9/L$, and for C-reactive protein concentration – < 5 mg/L.

Примечание: * – медиана (минимум–максимум) для количественных переменных с нормальным распределением; ** – абсолютные значения (%); *** – средние значения $\pm$ стандартное отклонение (минимум–максимум); референсные значения: для общего числа лейкоцитов – $(4,0-11,0) \times 10^9 / л$, для абсолютного числа лимфоцитов – $(1,5-4,5) \times 10^9 / л$, для концентрации С-реактивного белка – < 5 мг / л.

Statistical analysis

Parameters with a normal distribution are presented as mean values $\pm$ standard deviation, those without a normal distribution are presented as a median (minimum–maximum). Qualitative variables are presented in terms of frequency and percentage distribution. The statistical software package Statistica, version 13 was used for the analysis.

At the autopsy a pronounced plethora of internal organs, especially the lungs was revealed; in some patients, multiple fine hemorrhages in the parietal and visceral pleura, shock kidneys were observed. The lungs usually filled the entire chest cavity. The weight of the lungs was 1,450 (700 – 3,200) g. Gross examination revealed a typi-

Table 2
The frequency of occurrence of histological signs; n (%)
Таблица 2

Частота встречаемости гистологических признаков; n (%)

Histological signs	Number of cases
Edema	104 (84,55)
Starch bodies	9 (7,32)
Hyaline membranes	99 (80,49)
Cytotoxic pneumocyte changes	63 (51,22)
Bronchial epithelium desquamation	92 (74,80)
Bronchial epithelium metaplasia	35 (28,45)
Pneumocyte desquamation	91 (73,98)
Alveolar metaplasia	60 (48,78)
Megakaryocytes	37 (30,08)
Intraalveolar macrophages	89 (72,36)
Intraalveolar plasmatic cells, lymphocytes	73 (53,35)
Intraalveolar neutrophils	40 (32,52)
Intraalveolar erythrocytes	93 (75,6)
Intrabronchial erythrocytes	15 (12,2)
Siderophages/haemosiderin in alveoli	46 (37,36)
Infarcts/hemorrhages	51 (41,46)
Thrombus in arteries	60 (42,78)
Thrombus in veins	31 (25,20)
Microthrombus (in capillaries, arterioles, venules)	12 (9,76)
Edematous myxoid stroma	11 (8,94)
Interstitial inflammation	69 (56,1)
Fibrin in alveoli	80 (65,04)
Fibrin in bronchi	6 (4,9)
Fibroblastic tissue	61 (49,59)
Fibrosis of alveolar septae	16 (13,01)
Alveolar capillary congestion	17 (13,82)
Acute swelling	15 (12,20)
Aspiration	3 (2,44)
Intraalveolar ossification	7 (5,69)
Vasculitis/microvasculitis	10 (8,13)
Bacterial pneumonia	30 (24,39)

cal picture of “shock lungs”: the lacquered appearance of the dark cherry surface of the lungs, the rubbery density of the tissue, in the section from dark cherry to brownish red in color (Figure 1).

A crimson, opaque, thick liquid, which was hardly squeezed out of the tissue, flowed from the cut surfaces. In some cases, areas of acute swelling were observed, more often in the anterior parts of the lungs. One could see atelectasis (diselectasis), hemorrhagic infarctions, as well as hemorrhages of various sizes, merging with each other, sometimes spreading on the whole lobes. In some patients, obstructing blood thrombi were found in the branches of the pulmonary arteries and veins. At later stages, the lungs were compacted; on the incision in these areas, the tissue was grayish or grayish-yellow in color (Figure 2).

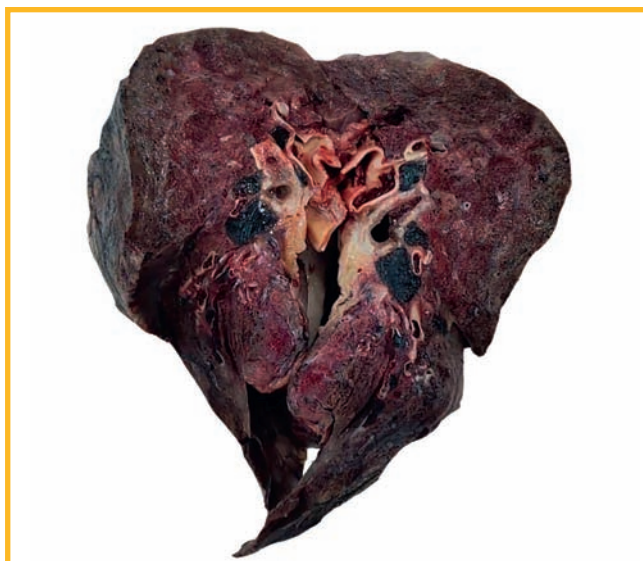


Figure 1. Gross cross section of the lung. "Shock lung": red surface with focal dark red areas (hemorrhage) under the visceral pleura

Рис. 1. Макропрепарат легкого. «Шоковое» легкое: на разрезе — ткань с чередованием участков красного и темного-красного цвета (кровотечения) под висцеральной плеврой



Figure 2. Gross cross section of the lung. Organizing pneumonia: large areas of gray-yellow color

Рис. 2. Макропрепарат легкого. Организующая пневмония: обширные участки серо-желтого цвета

Histological examination of the lungs revealed signs of viral interstitial pneumonia in the form of diffuse alveolar damage (DAP) in its various phases.

The exudative phase of DAP was detected in 54 (43.9%) deaths, the median duration of the disease in them was 11 (4 – 37) days. Histological examination in this group showed pronounced intraalveolar edema, hyaline membranes lining the contours of respiratory bronchioles, alveolar ducts, and sacs, alveoli in the form of strips of different thicknesses (Figure 3). There was damage to the epithelium associated with viral exposure desquamation of bronchial and bronchiolar epithelium, type I and II

pneumocytes, a proliferation of type II pneumocytes (Figure 4).

Most of the deceased showed signs of cytopathic damage to the epithelium with the appearance of ugly pneumocytes characterized by a variety of shapes, changes in the nucleus with the appearance of nucleoli, atypical mitoses; in some of the cells, enlightenment around the nucleus in the form of a halo, as well as round particles in the cytoplasm of cells, were found. In the lumens of the alveoli, small symplasts were often found, and in some of the dead multinucleated pneumocytes. Along with changes in the alveolar epithelium, epithelial cells with enlarged

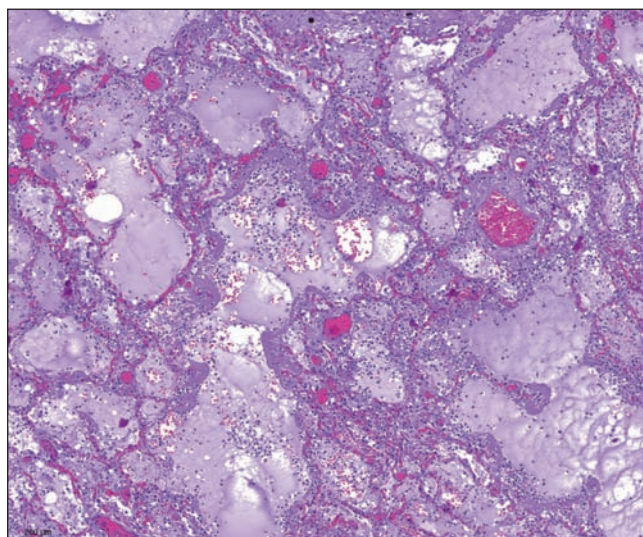


Figure 3. Intraalveolar edema with hyaline membranes lining the alveoli. H&E, × 100

Рис. 3. Внутриаальвеолярный отек и гиалиновые мембраны по контуру альвеол. Окраска гематоксилином и эозином, × 100

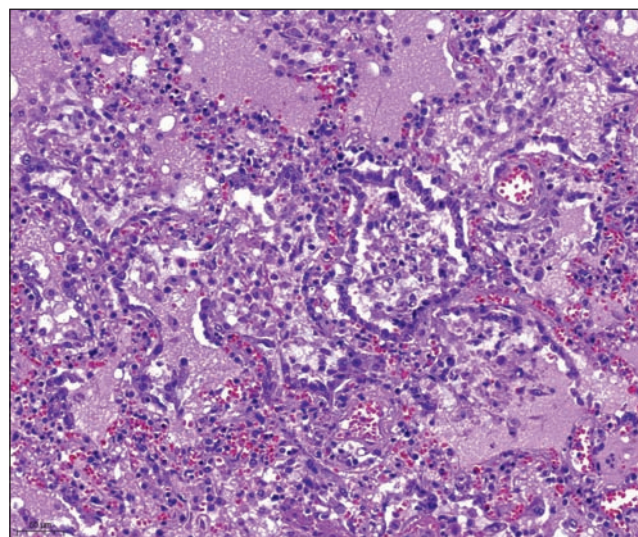


Figure 4. Intraalveolar edema, macrophages, desquamation of pneumocytes. H&E, × 200

Рис. 4. Внутриаальвеолярный отек, пласты десквамированного альвеолярного эпителия и макрофаги в просветах альвеол. Окраска гематоксилином и эозином, × 200

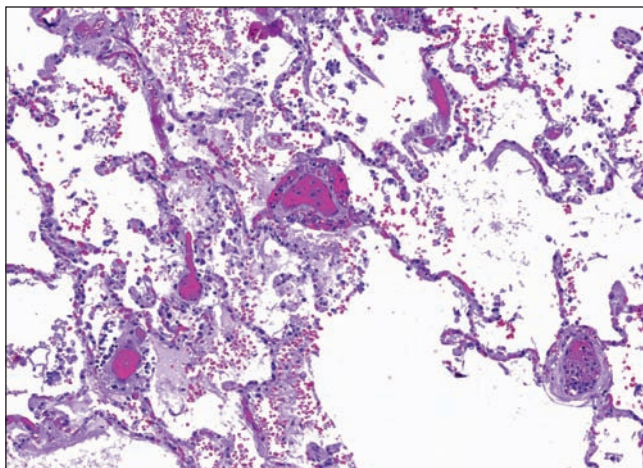


Figure 5. Mild intraalveolar edema, macrophages, lymphocytes, organizing thrombus in the arteriola, congestion of the arterioles. H&E, $\times 100$

Рис. 5. Небольшой внутриальвеолярный отек, макрофаги, лимфоциты в просветах альвеол, организующий тромб в артериоле, полнокровие артериол. Окраска гематоксилином и эозином, $\times 100$

nuclei were observed among the desquamated bronchial epithelium. In some cases (6 deaths), fibrin was found in the lumens of the bronchi and bronchioles. Some patients were found to have blood vessel's congestion (branches of the pulmonary arteries and veins, capillaries of the interalveolar septa) with damage and desquamation of endothelial cells, with the sludge of erythrocytes, organizing and fibrin thrombi (Figure 5), foci of perivascular hemor-

rhages, erythrocyte accumulation in the bronchial lumen. A third of the deceased from this group had focal hemorrhages and/or hemorrhagic infarctions. In the vascular endothelium of patients with COVID-19, overexpression of FVIII was found (Figure 6). Interstitial inflammation in this phase was represented by lymphoid infiltration of the interalveolar septa. In some cases, there was a rather pronounced intraalveolar accumulation of lymphocytes and macrophages. In rare cases, phagocytosed cell fragments and erythrocytes were observed in the cytoplasm of alveolar macrophages (Figure 7).

The proliferative phase of DAP was detected in 21 (14.63%) dead with a disease duration of 17 (9 – 23) days and was characterized, along with the changes described above, by the appearance of intraalveolar fibrin accumulations of varying degrees of maturity; edema of interalveolar septa of varying severity, with their infiltration by lymphocytes, plasma cells, macrophages, sparse neutrophils. In this phase of the disease, some patients were found to have myxoid edematous stroma in the interalveolar septa and perivascular spaces. There was a proliferation of fibroblasts, as well as deposits of collagen in the walls of the alveoli. In some patients, interstitial inflammation was quite pronounced, which was manifested by an enlargement of the alveolar septa. In this phase, the organization of fibrin was observed with the appearance of scattered fibroblasts, a proliferation of fibroblastic polypoid tissue in the lumens of the alveoli and respiratory bronchioles. In some patients, starch bodies were found in the alveoli as a result of prolonged edema.

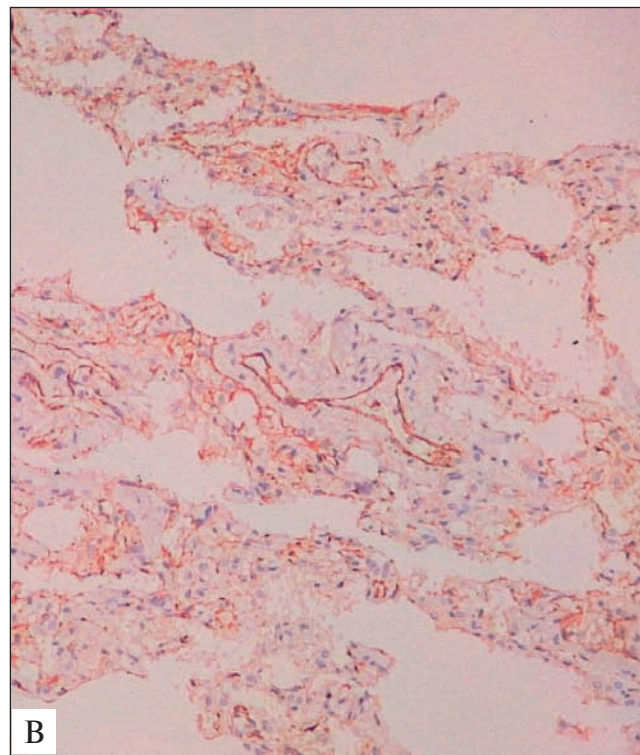
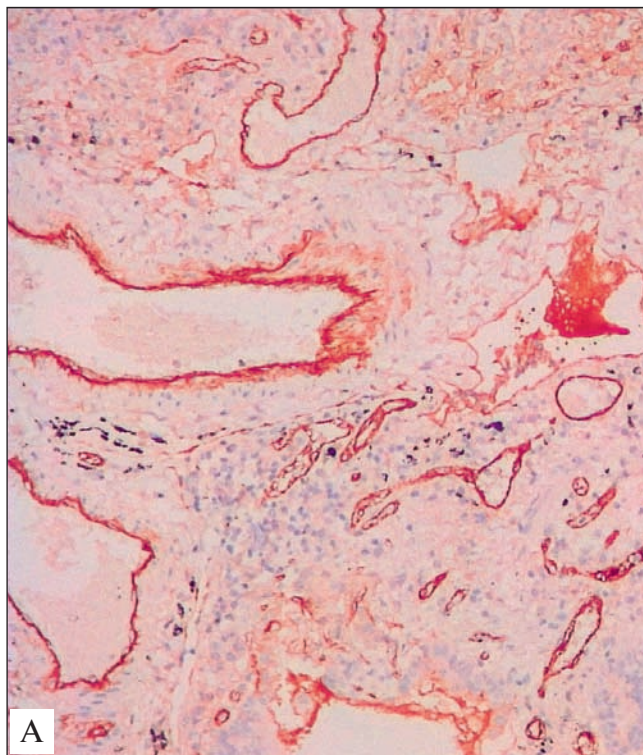


Figure 6. FVIII expression in endothelium: A, COVID-19 viral pneumonia; B, Control surgical material from the patient operated for lung cancer, unaffected area). IHC, $\times 200$

Рис. 6. Экспрессия FVIII в эндотелии сосудов: А — при вирусной пневмонии COVID-19; В — в контрольном наблюдении (операционный материал пациента, оперированного по поводу рака легкого, неизмененный участок ткани). Иммуногистохимическое окрашивание, $\times 200$

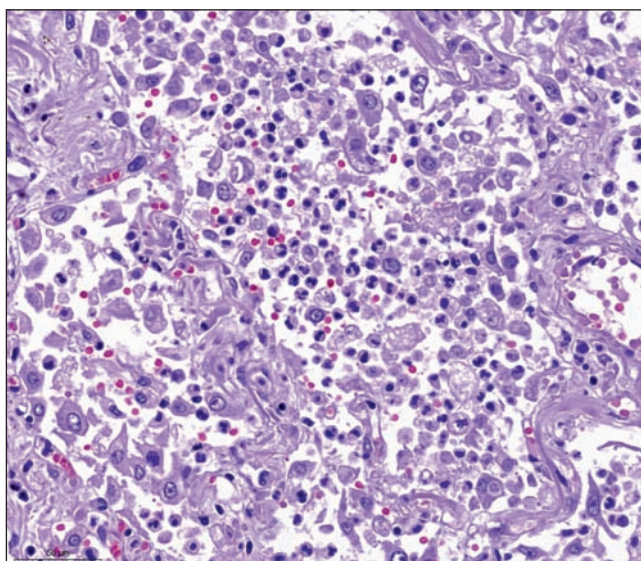


Figure 7. Intraalveolar accumulation of desquamation of pneumocytes with cytopathic changes, macrophages, autophagy: cell fragments in the cytoplasm of macrophages. H&E, $\times 250$

Рис. 7. Скопления в просветах альвеол десквамированных альвеолоцитов с цитопатическими изменениями, макрофагов, аутофагия: клеточные фрагменты в цитоплазме макрофагов. Окраска гематоксилином и эозином, $\times 250$

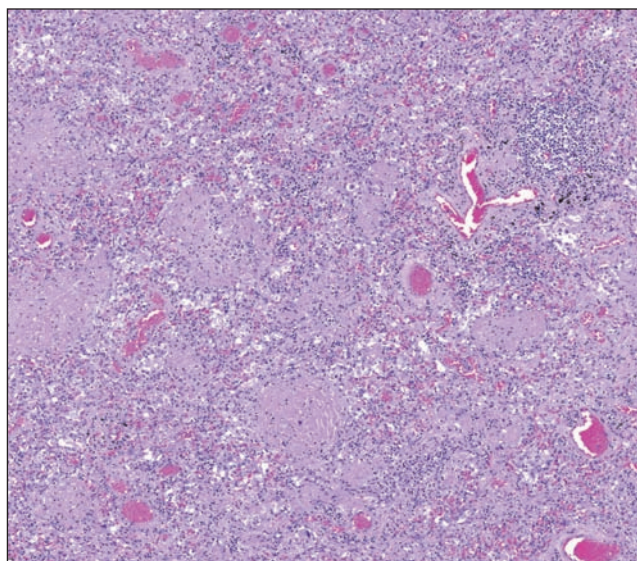


Figure 8. Intraalveolar fibroblastic tissue in the form of glomeruli, the focus of lymphoid infiltration. H&E, $\times 40$

Рис. 8. Фибробластическая ткань в просветах альвеол в виде клубочков, очаг лимфоидной инфильтрации. Окраска гематоксилином и эозином, $\times 40$

Intraalveolar accumulation of macrophages, lymphocytes, and plasma cells, more often found in the exudative phase, was also detected in some of the deceased in the proliferative phase of the disease. The last was characterized by the presence of reparative changes in the bronchiolar and alveolar epithelium in the form of proliferation of type II pneumocytes and squamous cell metaplasia. In some patients, focal areas of young connective tissue

in the form of “glomeruli” were found (Figure 8). There were also areas of fibrotic atelectasis, consisting of delicate connective tissue with a small number of collagen fibers and smooth muscle proliferation (Figure 9). However, no significant fibrosis with collagen deposition was found in any of the dead. In 7 out of 54 deaths with signs of the proliferative phase of DAP, fragments of bone tissue were found within alveoli, with localization in one case among desquamated and metaplastic pneumocytes.

With COVID-19 infection, a combination of exudative and proliferative phases of diffuse alveolar damage was often observed in 48 (39.02%) dead, the median duration of the disease was 15 (11 – 65) days. So, in these cases, in some areas of the lung, there was an acute process with the presence of edema and hyaline membranes, in others, signs of a proliferative phase were revealed the organization of fibrin, foci of organizing pneumonia, sometimes quite abundant or foci of granulation tissue.

In some patients with a prolonged course of the disease (more than 15 – 20 days), in areas of the lung with typical signs of proliferative changes, edema, hyaline membranes and pronounced desquamation of pneumocytes, including those with signs of cytopathic changes, were revealed (Figure 10). With a long course of the disease, the appearance of siderophages in the alveoli was observed, as well as the deposition of iron-containing pigment in the endothelium and the vascular wall.

Histological changes, which could indirectly indicate the impairment of coagulation, namely the appearance of intraalveolar hemorrhages, blood clots in pulmonary arteries and veins, were found in all phases of the disease. Lymphoid infiltration of the vessels with sparse cells as minimal signs of vasculitis was found in 10 deceased (Figure 11), while acute vasculitis and endotheliitis were observed only in cases complicated with bacterial

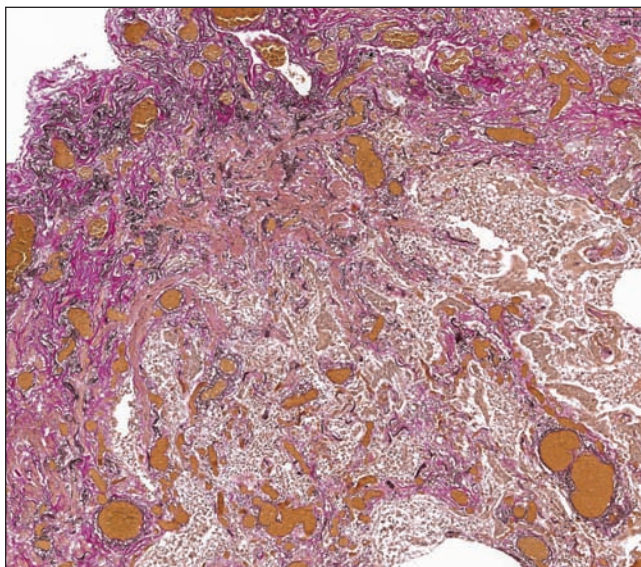


Figure 9. Subpleural fibrosis: connective tissue with a small number of collagen and elastic fibers, smooth muscle proliferation, angiomas. Stained with picrofuchsin by Van Gieson, $\times 50$

Рис. 9. Подплевральный участок фиброза: соединительная ткань с небольшим числом коллагеновых и эластических волокон, пролиферацией гладких мышц, ангиоматоз. Окраска пикрофуксином по Ван Гизону, $\times 50$

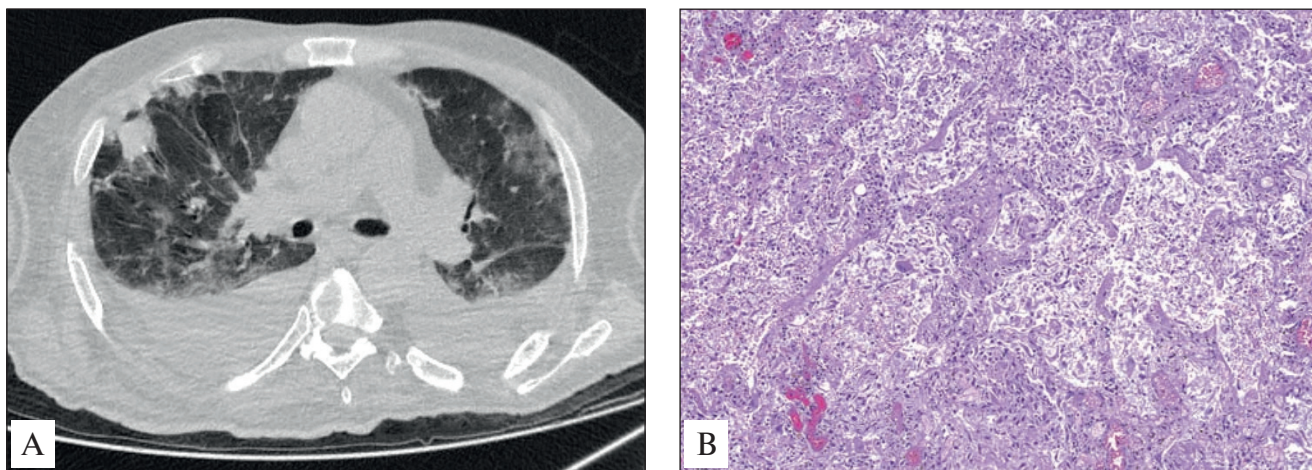


Figure 10. Patient 70 years old. SARS-CoV-2+. The duration of the disease is 65 days. The exudative with proliferative phase of diffuse alveolar damage: A, Computer tomogram of the lungs. Disease progression: foci of heterogeneous “ground-glass” opacity in the lingular of the left lung, areas of the round shape consolidation in the cortical zones of the right lung, bilateral pleural effusion; B, Fibroblastic tissue, desquamated pneumocytes with cytopathic changes, macrophages in the lumens of the alveoli, fibrosis of the alveolar septa. H&E, $\times 100$

Рис. 10. Пациент 70 лет. SARS-CoV-2+. Продолжительность заболевания — 65 дней. Экссудативно-пролиферативная фаза диффузного альвеолярного повреждения: А — компьютерная томография легких. Прогрессирование заболевания (неоднородный участок уплотнения по типу неоднородного «матового стекла» в языковых сегментах левого легкого, участки консолидации округлой формы в кортикальных отделах правого легкого, двусторонний плевральный выпот); В — фибробластическая ткань, десквамированный альвеолярный эпителий с цитопатическими изменениями, макрофаги в просветах альвеол, фиброз межальвеолярных перегородок. Окраска гематоксилином и эозином, $\times 100$

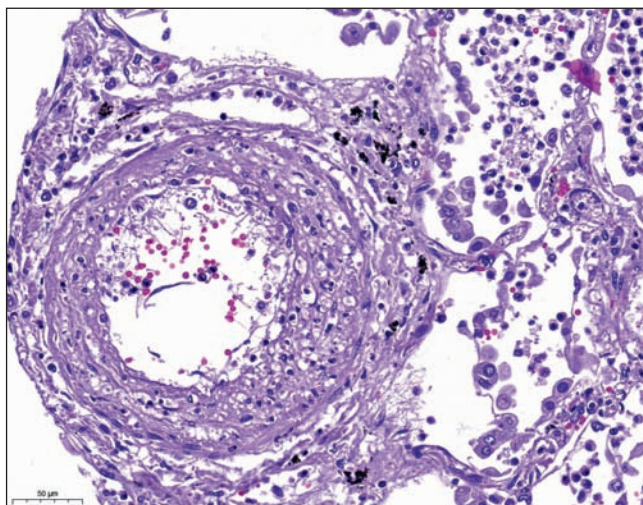


Figure 11. Immune inflammation in the vessel wall: lymphocytes in the intima and lumen of the branch of the pulmonary artery, reticular fibrin. H&E, $\times 100$

Рис. 11. Иммунное воспаление в стенке сосуда: лимфоциты в интима и просвете ветви легочной артерии, сетчатый фибрин. Окраска гематоксилином и эозином, $\times 100$

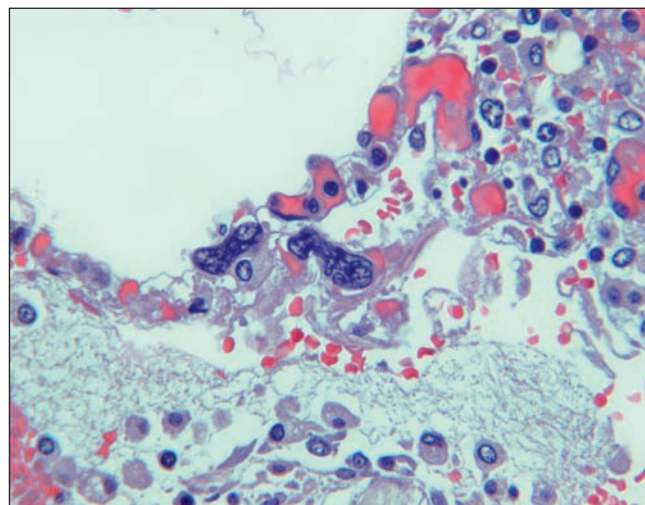


Figure 12. Megakaryocytes in the capillaries of intraalveolar septa, scanty macrophages and filaments of fibrin in the lumen of the alveoli. H&E, $\times 100$

Рис. 12. Мегакариоциты в капиллярах межальвеолярных перегородок, единичные макрофаги и нити фибрина в просвете альвеолы. Окраска гематоксилином и эозином, $\times 100$

pneumonia. In the capillaries of the interalveolar septa, megakaryocytes were found in more than one-third of the observations (Figure 12). In three cases of dead with confirmed COVID-19 infection (the duration of their disease was 4, 27, and 32 days, respectively), only minimal signs of intra-alveolar edema with single hyaline membranes were found in the lungs (Figure 13). At the same time, sludges of erythrocytes were found in the capillaries of the interalveolar septa, as well as fibrinous microthrombi or sludge of erythrocytes with their partial lysis and in the pulmonary arteries and veins.

Discussion

This study analyzed autopsy material of 123 deaths with a new coronavirus infection COVID-19 for the period from March 20 to June 6, 2020. At the beginning of our work, there were only a few descriptions of the lung pathology caused by the SARS-CoV-2 virus in the literature. To date, about 30 papers have been published, however, our study presents the analysis of the largest autopsy material to date.

A severe course of viral infection is characterized by the development of viral interstitial pneumonia, the typ-

ical morphological manifestation of which is diffuse alveolar damage. Histological changes in COVID-19 are similar to those previously described in severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and influenza A(H1N1) [7–9].

The most impressive feature of the morphological manifestations of COVID-19 is, in our opinion, is the discrepancy between the duration of the course of the disease and the phase of DAD. So, the changes characteristic of the exudative phase were observed on the 3rd – 37th day of the disease, and in some patients, the signs of proliferation could be detected as early as on the 7th day after the onset of symptoms. The latter fact can probably be explained by the fact that some patients have a long period of an asymptomatic or almost asymptomatic course of the disease. Besides, in 41.46% of cases, we identified a combination of exudative and proliferative phases of the disease. In a study by *A.N. Duarte-Neto et al.* a combination of exudative and proliferative phases of the disease was found in 8 out of 10 deaths [7]. The authors believe that this is due to the temporal evolution of the damage, as well as to mechanical ventilation. We suppose that a distinctive clinical course of the disease may be a possible explanation for this phenomenon. It is well known that in some patients a temporary improvement in the condition, as well as clinical and laboratory parameters, is followed by a repeated deterioration, which is probably associated with the sinusity of the virus replication process in the epithelium of the lower respiratory tract and pneumocytes. This can also explain the fact that in some patients in the late proliferative phase of diffuse alveolar damage, we observed desquamation of the alveolar epithelium with marked cytopathic changes (see Figure 10). It cannot be ruled out that this may be due to the long-term persistence of the virus, which can be detected in the lung tissue for many days and could be a trigger for repeated lung injury and disease progression [10, 11]. However, in some patients in the late phase of the course of the disease, the viral RNA is no longer detected in the material of nasopharyngeal smears. In our opinion, this temporal heterogeneity distinguishes the course of COVID-19 from other types of viral pneumonia. During the epidemic caused by the influenza A(H1N1) virus, morphological changes corresponded to the duration of the disease and the phases of DAD [12].

Cytopathic changes in the epithelium are most likely due to direct viral cell damage. Bronchiolar epithelium, pneumocytes I and, predominantly, type II express receptors for angiotensin-converting enzyme-2 (ACE2), which allows the virus to enter the cell. The SARS-CoV-2 virus has been detected in the alveolar epithelium in a number of studies [11, 13]. Multinucleated pneumocytes are not characteristic of the influenza virus, they have also not been described in SARS and MERS, however, some authors indicate their presence in COVID-19 infection [14, 15]. The appearance of multinucleated epithelial cells probably reflects an impairment of the process of cell proliferation and normal epithelial repair. However, such cells were uncommon in our material.

The issue of viral damage to lymphocytes, mainly CD4⁺ T-cells, is discussed in the literature. Although there are no receptors for ACE2 on lymphocytes, there is an assumption that the virus can enter the cell through membrane fusion and endocytosis. As a result, some of the lymphocytes may die, as is assumed by apoptosis or pyroptosis [16]. The fragments of cells and erythrocytes which we identified in the cytoplasm of macrophages may be indirect evidence of apoptosis of lymphocytes, but this requires further confirmation. The detection of such macrophages may also be indirect evidence of massive activation of the macrophage system, partially similar to that in secondary hemophagocytic lymphohistiocytosis [17]. Previously, signs of hemophagocytosis were found in the lymph nodes, spleen, bone marrow, heart, and liver [18]. Such changes were revealed in the exudative phase, during a certain period of which the most pronounced intraalveolar accumulation of macrophages, lymphocytes, and plasmocytes is determined, along with inflammatory infiltration of interalveolar septa. It is seeming that this occurs in the phase of the “cytokine storm” accompanied by a prompt decrease in the absolute number of lymphocytes in the blood of patients.

A number of morphological studies based on autopsy material from dead with COVID-19 have demonstrated a high incidence of thromboembolic events in the lungs. Thus, in a study by *D. Wichmann et al.* [19], a high incidence of deep venous thrombosis is indicated, which amounted to 58% in a group of 12 deaths, in the work of *C. Edler et al.* in 40% in a group of 80 deaths [20]. Many studies have confirmed the high frequency of blood clots and microthrombi in the lungs [21, 22]. However, in our opinion, despite the available data on systemic coagulation, in most cases these changes in the lungs should be regarded as thrombosis, not thromboembolism (except for clearly identified thromboembolism at autopsy). We took into account the nature of the intravascular contents from sludge erythrocytes to fibrinous thrombi, as well as reticular fibrin in the lumens of blood vessels in some cases. We found the organized fibrinous thrombi in the pulmonary artery only in two cases. At the same time, a high frequency of intrapulmonary thrombosis and microthrombosis is shown in many studies [20, 21]. *M. Ackermann et al.* depicted the 9 times higher incidence of capillary microthrombosis in COVID-19 than in influenza A(H1N1) [20]. Using scanning and convection corrosion electron microscopy, the authors demonstrated the presence of viral particles in the vascular endothelium of the lungs, as well as signs of capillary angiogenesis.

Coagulopathy is common in severe COVID-19. So, in a study of 191 patients with COVID-19, 50% of the deceased had signs of thrombotic disorders versus 7% in the survivors. A high concentration of D-dimer (> 1,000 µg/mL) is an unfavorable prognostic factor associated with a high risk of death [22]. However, it has been shown that in patients with COVID-19 there is no significant decrease in the proportion of platelets and the concentration of fibrinogen. As a rule, patients with new coronavirus infection do not develop disseminated intravascular coagulation syndrome (DIC). The latter was de-

tected in only a small portion of patients in the terminal stage of the disease. In this regard, coagulation syndrome in COVID-19 was proposed to be called “diffuse pulmonary intravascular coagulopathy” [17, 23].

Activation of the coagulation system has been described for some viral pneumonia, including coronavirus, as well as those caused by the Ebola virus, HIV, and dengue virus [24, 25]. Coronavirus infection can be a trigger for disturbance of the coagulation system, the pathogenetic mechanisms of which are complex and include endothelial dysfunction characterized by increased production of von Willebrand factor, systemic inflammation with activation of *Toll*-like receptors, as well as activation of procoagulant factors. It is assumed that the process of thrombus formation may be associated with hypoxia, which causes activation of transcription factors, and immune damage associated with the action of antiphospholipid antibodies [13, 25–28]. Some authors point to the presence of endotheliitis, including leukocytic, as a cause of endothelial damage [29]. In our observations, in 8.13% of patients, infiltration with sparse lymphocytes of the blood vessel's wall was detected. Thereby, the picture does not fit into the common picture of vasculitis; apparently, it is worth talking about immune vascular damage that develops after viral and cytokine damage [17].

Congestion and microthrombosis of the capillaries of the alveolar septa are one of the vivid morphological signs of viral pneumonia COVID-19 [19, 30]. *C. Magro et al.*, *C. Edler et al.* showed that in patients with plethora and microthrombosis of capillaries, the signs of diffuse alveolar damage were less pronounced [3, 20]. Such changes can be detected already in the early stages of the disease. However, in our work, in 4 patients, plethora and microthrombosis of the capillaries of the in-

teralveolar septa in the presence of a minimal severity of edema and scarce hyaline membranes were detected 5 – 35 days after the onset of symptoms. In these patients, CT changes in the lungs indicated the presence of minimal viral pneumonia (see Figure 13). We assume that one of the possible causes of death in COVID-19 infection is impaired coagulation in the late stages of the disease, with almost complete resolution of viral pneumonia. The mechanisms of such damage require further study and clarification.

The appearance of megakaryocytes in the capillaries of the alveolar septa, in all likelihood, is also a sign reflecting an impairment of coagulation. Megakaryocytes in the capillaries of alveolar septa have been described by some authors in infection caused by SARS-CoV-2 [11, 13, 17, 31]. In the work of *V.V. Kungurova*, *S.V. Khasanyanov* it was shown that megakaryocytes can be found in the capillaries of alveolar septa and other organs in shock conditions of various etiologies [32], including sepsis [33]. Normally, megakaryocytes rarely leave the bone marrow, however, under the condition of hypoxia, the appearance of these cells in the capillaries of the lungs indicates intense hematopoiesis and can lead to local platelet formation. Besides, there are suggestions that some viruses, including dengue virus, can directly damage megakaryocytes, leading to impaired platelet production and thrombocytopenia [34]. The latter is one of the laboratory signs of COVID-19.

Squamous metaplasia of the bronchiolar and alveolar epithelium has been previously described in other viral pneumonia SARS, MERS, influenza A(H1N1). Some authors point to pronounced squamous cell metaplasia in COVID-19 [7, 22, 31, 35], which is most likely associated with direct viral damage to the epithelium, as well as with

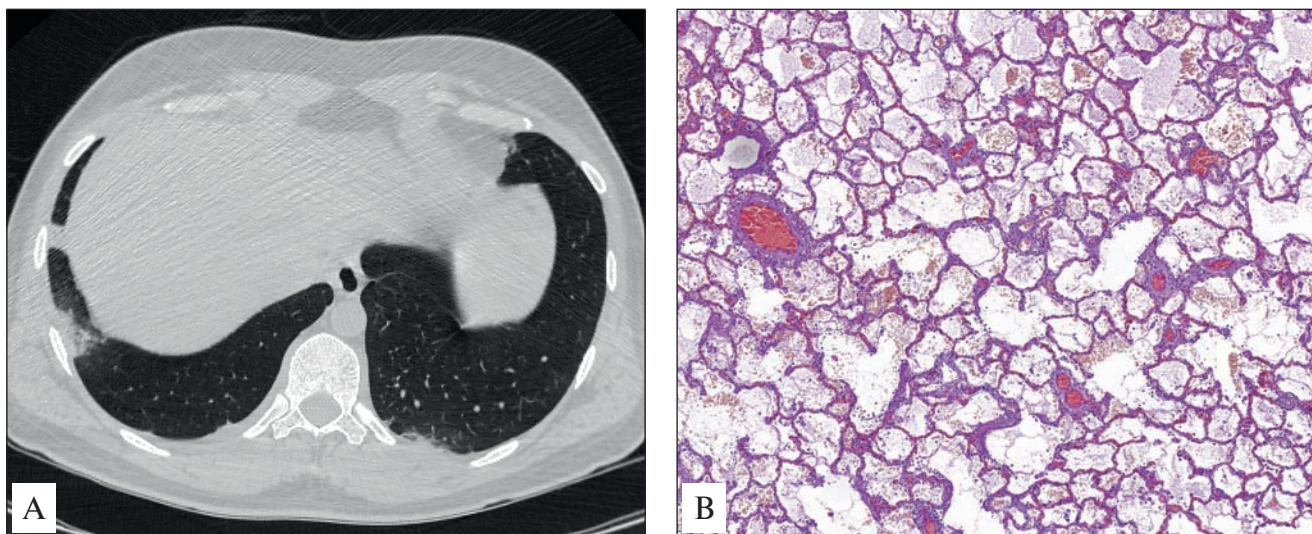


Figure 13. Patient 34 years old. SARS-CoV-2+. Concomitant disease: dilated cardiomyopathy. Disseminated intravascular coagulation: A, Computer tomogram of the lungs: Residual effects of viral pneumonia: subpleural site of heterogeneous consolidation in the lower lobe of the right lung, subpleural linear opacity in the lower lobe of the left lung; B, Minimal signs of intra-alveolar edema, single hyaline membranes, capillary congestion, erythrocyte sludges in the branches of the pulmonary artery

Рис. 13. Пациент 34 лет. SARS-CoV-2+. Сочетанное заболевание: дилатационная кардиомиопатия. Синдром диссеминированного внутрисосудистого свертывания. А — компьютерная томография легких. Остаточные явления вирусной пневмонии: субплевральный участок неоднородной консолидации в нижней доле правого легкого, субплевральное линейное уплотнение в нижней доле левого легкого; В — минимальные признаки внутриальвеолярного отека, единичные гиалиновые мембраны, полнокровие капилляров межальвеолярных перегородок, сгустки эритроцитов в ветвях легочной артерии

the effect of oxygen during ventilation in patients with the severe course of the disease. Previously, it was shown that the protein E of the coronavirus leads to damage to inter-cellular contacts [36] and subsequent impairment of repair processes.

In our study, in 5.7%, bone metaplasia was observed in the lungs during the proliferative phase of diffuse alveolar damage in COVID-19. The presence of bone metaplasia in the lungs with a new coronavirus infection is indicated by some authors [15]. The processes of calcification and ossification in the lungs can be associated with an increase in the serum concentration of calcium and phosphate, the activity of alkaline phosphatase, as well as with a local disturbance of pH in the tissue. Additional studies are needed to clarify the possible pathogenetic mechanisms of such a rapid (within 1 – 1.5 months) formation of calcifications and ossifications in the lungs in viral pneumonia [37].

In our study, the frequency of detection of histological signs of acute pulmonary distention was 12.2%, in half of the observations with invasive ventilation of the lungs, and in half in conditions of high-flow mask ventilation with oxygen. Probably, the toxic effect of oxygen can cause damage to the surfactant lining of the alveoli with the subsequent focal expansion of the alveoli and alveolar ducts.

Although the most dramatic changes in COVID-19 occur in the lungs, as a result of viral exposure, as well as the development of a systemic inflammatory response and thrombohemorrhagic syndrome, damage to other organs occurs. However, we did not set out to describe them as our goal in this work [38].

Conclusion

The pathology of the lungs in COVID-19 corresponds to viral interstitial pneumonia in the form of DAD. An analysis of 123 cases revealed a discrepancy between the duration of the course of the disease and the phase of DAD. In a significant portion of the patients, a combination of exudative and proliferative phases of the disease was found. Histological signs are described that indirectly indicate an impairment of the coagulation system during COVID-19.

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