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Lung lesions caused by COVID-19 in comparison with bacterial pneumonia and influenza pneumonia: pathomorphological features

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Abstract

This review aimed to summarize the literature data regarding the pathomorphology of lung lesions in COVID-19 and compare it with lung lesions in bacterial pneumonia and pneumonia caused by influenza virus. The analysis of scientific literature containing studies of domestic and foreign authors of different years related to morphology and anatomical pathology of lung injury was carried out. Special attention was paid to the data devoted to COVID-19 obtained between 2019 and 2021. Based on the study, the main aspects of lung lesions were identified and grouped into blocks depending on the etiology of the process. The review collects and summarizes information on etiology, pathogenesis and stages of disease development, outcomes and morphological picture during the autopsy of patients with bacterial pneumonia, influenza pneumonia and COVID-19 pneumonia. The common features and differences in the course, outcomes and typical morphological findings, most characteristics for each of the diseases were presented in the table. There is a great similarity of morphological findings in influenza pneumonia and COVID-19 pneumonia despite the background of the difference in their epidemiology. Most Russian and foreign authors agree that a key factor in the pathogenesis of the development of COVID-19 is the presence of a specific receptor-mediated pathway of penetration into the cells of the respiratory epithelium. According to most authors, the main morphological difference that determines the severity and unfavorable outcome of COVID-19 is angiopathy and microthrombosis of the pulmonary capillary bed, which aggravate the typical picture of viral pneumonia.
Keywords: inflammation, fibrosis, thromboembolism, microembolism, interstitium, alveoli.

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Introduction. During the coronavirus disease 2019 (COVID-19) pandemic caused by the new coronavirus, a detailed investigation of this new disease has begun. The amount of scientific data accumulated to date is very extensive and is constantly being replenished. However, there is a need to characterize the disease from the standpoint of pathological anatomy to determine the possible causes of the severity of the disease course and predictors of an unfavorable outcome. This review analyses the pathogenesis and typical morphological signs of pneumonia of various etiologies (bacterial and viral) for comparison with the pathogenesis and anatomicopathological findings of biopsy and autopsy materials from patients with COVID-19. The extensive and rapid spread of COVID-19 globally continues up to the present day, which makes this review relevant.

This review aimed to summarize the literature data on the pathomorphology of lung damage in COVID-19 and compare them with lung damage in bacterial pneumonia and pneumonia caused by the influenza virus.

Bacterial pneumonia. *Sources and pathogens*. Nearly all pathogenic or opportunistic microorganisms that have entered the lower respiratory tract can become causative agents of bacterial pneumonia. Traditionally, bacterial agents of pneumonia are divided into “typical” and “atypical.”

Typical pathogens include *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus*, group A streptococci, *Moraxella catarrhalis*, and anaerobic and aerobic gram-negative bacteria. Atypical pathogens include *Legionella pneumophila, Mycoplasma pneumoniae, Chlamydia pneumonia*, and *Chlamydia psittaci* [1].

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According to data from international and Russian authors, obtained from the PubMed database and online archives of journals indexed by Scopus and the Higher Attestation Commission, *S. pneumoniae* is the most common cause of community-acquired pneumonia (CAP), which accounts for 30%–50% of the cases. The proportion of mixed infections usually does not exceed 10%; however, in some studies, this indicator reaches 27%, and 54% in patients aged >60 years [1–4].

Golubev noted that despite the predominance of pneumococci in the range of the pathogens, they are identified as monoflora in <20% of cases of bacteriologically confirmed CAP. Moreover, >80% of CAP cases were associated with combined microbial flora [5].

The second most common causative agent of CAP as a monoflora is *M. pneumoniae* (11% and 22% of clinically and radiologically confirmed cases, respectively). Other bacteria are less significant in terms of pneumonia pathogens [6].

In most cases, the source of CAP is a sick person or an asymptomatic carrier of an infectious agent. Some pathogens, such as *Legionella* and *Chlamydia*, can be transmitted to humans through contaminated air-conditioning systems or from birds and certain animals [1].

For hospital-acquired pneumonia, the most typical causative agent is the combination of *S. aureus* (methicillin-resistant *S. aureus*) with *Pseudomonas aeruginosa, Acinetobacter baumannii*, and *Escherichia coli*. *S. aureus* and *Klebsiella pneumoniae* were identified most often as etiological factors in purulent destructive pneumonia [5].

Mechanism of damage and target tissue of the pathogen (e.g., pneumococcal CAP as the most common). The development of pneumonia is associated with a disruption of the delicate balance between the microorganisms in the lower respiratory tract and local and general immunity. Disorders of the systemic immune response, mucociliary clearance, cough reflex, and drainage function of the bronchi are crucial to the pathogenesis of pneumonia [7].

If one or more protective factors are impaired, pathogens can enter the lower respiratory tract. When bacteria enter the alveoli, they initially attach to the alveolar wall and spread not only bronchogenically but also from one alveolus to another alveolus through Cohn's pores [8]. Attached and free bacteria proliferate in the lower respiratory tract, causing typical clinical and morphological changes in the lung parenchyma, depending on the pathogen, immune status of the organism, morphological aspects of the inflammatory reaction, and scope of lung tissue damage [9].

The causative agents of bacterial pneumonia have no tropism for the epithelium or specific receptors in the lower respiratory tract. They reproduce opportunistically in the lumen of the middle and small bronchi, where there is a favorable environment resulting from the destruction of protective barriers. Consequently, nonspecific inflammation develops, which is associated with factors of pathogenicity and the cytotoxic response of the complement system [10].

Stages of the pathological process development (e.g., pneumococcal pneumonia). In the development of pneumococcal CAP, pathophysiologically, four stages are usually distinguished (i.e., adhesion, invasion, inflammation, and shock) [8]. Herein, we will consider the course of bacterial pneumonia using a classical scheme of the course of lobar pneumococcal pneumonia [11, 12].

– Stage of hot flush (day 1) with hyperemia, microbial edema, and diapedesis of erythrocytes into the lumen of the alveoli.

– Stage of red hepatization (day 2) with massive exudation into the lumen of the alveoli.

– Stage of gray hepatization (days 4–6) is manifested by the accumulation of fibrin, neutrophils, and phagocytic macrophages.

– Resolution stage (days 9–11) is manifested by the resorption of fibrinous exudates in the alveoli, fibrinous overlays on the pleura, and cleansing the airways from pneumococci.

Outcomes of pneumococcal CAP. According to Kothe et al. [13], the 30-day mortality from CAP was 6.3%, which was significantly higher among older patients (10.3%) than in younger patients. Age ≥65 years, living in a nursing home, interruption of the treatment course, congestive heart failure, cerebrovascular diseases, and chronic liver disease were indicated as significant risk factors for lethal outcomes.

In a cohort study by Fine [14], the outpatient mortality rate was significantly lower than the inpatient mortality rate (0.6% and 8%, respectively). The course of pneumonia in outpatients was more favorable, with a lower incidence of complications (8%) than in inpatients (69% of patients had one or more complications). Inpatient treatment was associated with a later return to normal activities (within 30 days of illness onset, 82% versus 95% of outpatients) and longer persistence of pneumonia-related symptoms (86% of patients retained one or more symptoms for 30 days versus 76% for outpatients).

In the CAP group, acute respiratory distress syndrome (ARDS) developed in 83.3% (5 cases) against the progression of inflammation in the lungs. In the hospital-acquired pneumonia group,

ARDS was recorded in 21 of 30 cases and in 76.2% of 16 cases; ARDS preceded the pneumonic infiltration [5].

Madani et al. [15] conducted a retrospective review of all postmortem reports from 1991 to 2000 at King's College Hospital, London. Fatal pulmonary embolism was recorded in 5.2% cases of lethal outcomes in patients with pneumonia, while 80% had no history of surgery and were >60 years old. Thromboembolia of the pulmonary artery developed within 6 weeks after acute lung disease.

The mortality rate of patients with immunocompromised status was higher, and their average age was less than that of patients with normal immune status. According to Terrabuio Junior [16], in patients with bilateral pulmonary infiltrates and secondary interstitial pneumonia, malignant tumors (48%), sepsis (48%), condition after transplantation (14%), and diabetes mellitus (13%) were the underlying diseases. The median age of the patients who died of pneumonia in a state of immunosuppression was 51 years. The median age of the patients who died from pneumonia and had a normal immune status was 75 years [17].

A similar distribution was found by Juric et al. [18] in their autopsy of 3117 corpses. The most frequent causes of lethal outcomes were cardiovascular diseases (40.9%), followed by malignant neoplasms (25.2%) and infections (12.9%). Moreover, bacterial pneumonia was not diagnosed *in vivo* in 67.5% of the cases.

Pathomorphological characteristics. Clinical and morphological analyses of changes in the lungs of patients who died from CAP or hospital-acquired pneumonia in Russia and in other countries demonstrated similar patterns [5, 11, 12].

CAP is characterized by a more pronounced inflammatory reaction (in terms of the incidence of infiltrates and time of formation), and areas with alveolar edema and hemorrhages were adjacent to the foci of inflammation. Areas of organization were identified more often. Interstitial edema was rare and moderate.

In hospital-acquired pneumonia, alveolar edema (which was of a total or subtotal nature) was predominant, as well as infiltration of interalveolar septa by segmented leukocytes (beyond the foci of inflammation) [5, 11, 12].

The postmortem examination of deceased patients revealed pulmonary edema of varying severities in 69.2% of cases of CAP and 76.7% of cases of hospital-acquired pneumonia. A plethora of vessels located in the bronchial wall was histologically noted. Beyond the zone of inflammation in the lungs, widespread alveolar edema, extensive alveolar hemorrhages, and a plethora of capillaries and veins were noted. With the development of ARDS in hospital-acquired pneumonia, inflammatory changes of a purulent-edematous nature, and fibroplastic reactions were common [5].

In patients with pneumonia and sepsis, histological examination revealed widespread pulmonary edema with severe hyperemia of all vessels, as well as hyaline membranes and desquamated epithelium in the lumen of the alveoli, and areas of necrosis surrounded by inflammatory infiltrates. Among areas with accumulations of blood cells, colonies of microorganisms (cocci) were noted. There were mixed thrombi in the lumen of a part of the vessels [5, 12].

With CAP, the development of unilateral purulent pleurisy was often recorded, while patients with hospital-acquired pneumonia mainly had bilateral serous pleurisy [5].

The autopsy results did not reveal a clear dependence of the observed morphological changes in the lungs on a specific causative agent of pneumonia; however, the prevalence of *S. aureus* is associated with the development of purulent hospital-acquired pneumonia [5, 11].

According to the results of the above studies, the pathomorphological presentations in bacterial pneumonia are quite homogeneous and similar to each other; however, they may differ depending on the disease stage and cases analyzed.

Influenza. *Sources and pathogens*. The source of the infection is a sick person. The disease is disseminated by airborne transmission. The causative agents of influenza are pneumotropic RNA-containing[1] viruses of three antigenically determined serological variants (A (A1, A2), B, and C) belonging to the *Orthomyxoviridae* family [11].

Mechanism of damage and target tissue of the pathogen. The influenza virus has a tropism for the epithelium of the upper and lower respiratory tract, which determines to some extent the severity of the infectious process. Electron microscopy revealed the accumulation of viral particles in the cytoplasm and nuclei of the epithelial cells of the respiratory tract, submucous glands, and pneumocytes. In this condition, the major targets of the influenza virus are type 2 pneumocytes and less often tissue macrophages [11, 19].

According to Taubenberger [20], the depth of infiltration of the virus along the bronchial tree is directly associated with the clinical severity of the disease course.

Primary adsorption, introduction of hemagglutinin (H), and neuraminidase (N) with the participation of surface viral proteins and viral replication

[1] RNA, ribonucleic acid.

under the control of RNA polymerase occur in bronchiolar, alveolar epithelial, and capillary endothelial cells, which leads to primary viremia. Given the cytopathic action of the virus, degeneration, necrosis, and desquamation of the epithelium of the upper respiratory tract occur, which leads to the possibility of secondary viremia and further development of the disease. In this case, the vasopathic (plethora, stasis, plasmorrhagia, and hemorrhage) action of the influenza virus and its ability to suppress the body's defense systems, such as the neutrophils and macrophages, and immune system as a whole are the most significant.

The vasopathic and immunosuppressive effects of the influenza virus determine the occurrence of secondary infection and the nature of local (rhinitis, pharyngitis, tracheitis, bronchitis, and pneumonia) and general (discirculatory disorders, dystrophy of parenchymal elements, and inflammation) changes [11]. In this case, viral replication occurs in pneumocytes, which directly, as well as indirectly through the inflammatory response of the host, leads to alveolar damage. This underlies diffuse alveolar damage (DAD), which represents the main mechanism of lung injury in influenza [21].

Stages of the pathological development in influenza virus pneumonia. There is no single, standard view on the morphological staging of the pathological process in pneumonia caused by the influenza virus. However, several authors have described similar signs inherent in developing viral pneumonia and indicated the approximate dates at which such changes were detected. Thus, early studies by Mulder [22] described changes characteristic of the initial stages of infection, which were detected in patients 2–4 days after the disease onset.

In her later work, Chartorizhskaya [23] determined more accurately the phases of the course of pneumonia in influenza infection, dividing them into early (3–9 days) and late (9–11 days) phases, based on the prevailing morphological changes in the lung tissue:

– Day 3 (exudative phase) manifested by diffuse intra-alveolar edema and fibrin polymerization.

– Day 6 (end of the exudative phase) manifested by diffuse alveolar edema resolution, squamous metaplasia of the epithelium of terminal bronchioles, accumulation of lymph–plasma–macrophage infiltrates in the interstitium, and formation of hyaline membranes.

– Day 10 (start of the proliferative phase) manifested by the proliferation of fibroblasts in the interstitium, phagocytosis, and lysis of hyaline membranes by alveolar macrophages.

Taubenberger [20] gave numerous examples of morphological changes and noted that the presentation described is specific for each patient and depends on many factors; thus, it is difficult to classify the process into stages.

Outcomes of pneumonia caused by influenza virus. Outpatient treatment of influenza-associated pneumonia is related to the lower rates of disease progression, complications, and mortality than the course of influenza requiring hospitalization. Lynfield et al. [24] described progression in 5.1% of outpatients and 21.6% of inpatients. In inpatients, progression was recorded in 12.8% of patients admitted to general wards and 53% of patients admitted to intensive care units. They noted [24] that age, longer duration of symptoms at study enrollment, and immunosuppression were predictors of disease progression.

Shieh [19] emphasized the significant role of secondary bacterial infections in the mortality of patients from influenza-associated pneumonia (>40%). *Pneumococcus* spp was the predominant microorganism among causative agents of complications. A correlation was also found between concomitant bacterial infections and shorter disease duration to lethal outcomes compared with uncomplicated influenza (in 80% of patients, the disease duration was <10 days).

Microbial associations as a significant part of thanatogenesis in influenza are described in a smaller number of cases (24%–26% of cases) in Russia than in other countries [23, 25, 26].

Chartorizhskaya [23] described the outcomes of influenza-associated pneumonia depending on the disease duration. According to their data, lethal outcomes occurred after day 7 of illness in 72% of cases. Less than 24-hour mortality was noted in 17.5% of the cases, and lethal outcomes during transportation and at home occurred in 3.5% of the cases.

According to Britto [27], the presence of concomitant diseases, such as chronic obstructive pulmonary disease, asthma, and cystic fibrosis, was associated with a higher probability of a severe form of influenza and a poor prognosis.

Pathomorphological characteristics. The most common findings during an autopsy of patients with pneumonia caused by the influenza virus are DAD signs, circulatory disorders, aggregation and sludge of corpuscles in the microvasculature, pronounced interstitial and unevenly expressed diffuse alveolar edema, and leukocyte infiltration, which are considered typical findings of viral pneumonia [20, 23, 28].

Bilateral thrombosis of the small branches of the pulmonary artery was noted in 24% of the cases [23, 28]. Diffuse intra-alveolar edema (days 2–3 from the disease onset), squamous cell metaplasia of the epithelium of terminal bronchioles, hyaline

membrane formation (days 6–7 from disease onset), proliferation of fibroblasts in the interstitium, and lysis of hyaline membranes by macrophages (days 10–12 from disease onset) were observed in the lumen of the alveoli.

In most cases on days 5–6, the authors have noted bacterial pneumonia, which was characterized by a typical morphological presentation with inflammation, purulent and hemorrhagic nature, and involvement of the pleura in the form of serous or fibrinous pleurisy with a pronounced hemorrhagic component. The alveoli contained purulent fibrinous or fibrinous, purulent, hemorrhagic exudates; the interalveolar septa were infiltrated by leukocytes; and there was a purulent fusion of some of them with microabscess formation [23].

Harms [28] also indicated the following as common autopsy findings: microthrombosis of the pulmonary artery branches, DAD, foci of hemorrhagic necrotizing bronchopneumonia, frequent involvement of the pleura in the inflammatory process, hyperplasia of type 2 pneumocytes, and hyaline membranes merging into a network of fibrin in the lumen of the alveoli or covering the epithelium defects [20, 28].

Taubenberger [20] noted at the resolution stage reparative fibrotic phenomena such as regeneration of the epithelial lining of the alveoli and bronchial tree with pronounced mitosis, squamous cell metaplasia, interstitial fibrosis of the alveolar walls, phagocytosis of erythrocytes by macrophages, and obliterating bronchiolitis with or without signs of organizing pneumonia.

Gladkov proposed a conditional division of influenza cases based on autopsy findings into five groups [29] given the heterogeneity of lung changes upon detailed study. The proposed groups reflect both the morphological nature of the injury and the details of the clinical course in association with the timing of the disease course. This indicates the complexity and multifactorial nature of the pathogenesis of influenza, even within the lesion caused by one single pathogen.

In a study of 15 patients with pneumonia caused by the H1N1 strain, Prasad et al. [30] emphasized that histopathological findings are usually located in the lungs, including signs of DAD in the form of mononuclear and neutrophilic infiltrates, thickening of the alveolar septa, intra-alveolar hemorrhage, pulmonary vascular obstruction, pulmonary edema, hyaline membrane formation, and desquamation of the bronchial epithelium.

COVID-19. *Sources and pathogens*. Coronaviruses (CoV) are single-stranded enveloped RNA viruses that cause respiratory diseases in humans and animals. These ubiquitous viruses cause diseases ranging from mild upper respiratory tract catarrh to severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Several cases of pneumonia reported in Wuhan, China, at the end of 2019 led to the identification of a new CoV, later designated the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent of COVID-19 [31].

Mechanism of damage and target tissue of the pathogen in COVID-19. The pathogen is characterized by the presence of a specific receptor related to the receptor for angiotensin-converting enzyme type 2 (ACE2). ACE2 receptors are expressed in the epithelium of the respiratory tract, pneumocytes, alveolar monocytes, vascular endothelium, epithelium of the gastrointestinal tract, urinary tract, macrophages, and other cells of organs and tissues, including the myocardium and some parts of the central nervous system. ACE2 receptors serve as functional receptors for SARS-CoV-2 and provide CoV access to the epithelial cells of the upper respiratory tract, where it is capable of the most active replication [32–35].

Yuki [36] suggested that CoV spread through the infected lung epithelium into the pulmonary vascular endothelium, which also expresses the ACE2 receptor. Other authors considered the gender difference in the expression of ACE2 receptor as one of the factors of higher mortality in male patients (105.2 ± 9.1 RFU/μL/h[2] in men versus 84.7 ± 6.9 RFU/μL/h in women, $p = 0.05$) [37].

Zayratyants [32] compared the course and progression of COVID-19 with SARS and noted the similarity of the viral replication in the lower respiratory tract with the development of secondary viremia, immune disorders, and hypoxia. This situation leads to damage in many target organs such as the heart, kidneys, and gastrointestinal tract, which cells express the ACE2 receptor. Thus, clinical deterioration is observed at week 2 from disease onset. However, the author considered the development of microangiopathy in the form of destructive productive thrombovasculitis and hypercoagulable syndrome, as well as damage to the organs of the immune system, as the key difference between the new CoV infection and SARS. Moreover, a persistent inflammatory response acts as a trigger of the coagulation cascade, which, in combination with direct viral damage to the endothelium of the microvasculature, aggravates the severity of the clinical course and worsens the prognosis.

A similar point of view is shared by several Chinese and European authors who have studied COVID-19 cases [33, 34, 36].

[2] RFU, relative fluorescence unit.

Chen [34] noted a disproportionately extensive lesion of the respiratory system and an unusually high proportion of older patients (55.8%) compared with SARS and MERS.

Lung tissue damage in COVID-19 is significantly attributed to the body's hyperergic immune response, accompanied by DAD and severe extrapulmonary lesions up to the development of septic shock [32].

Generally, the essence of lung damage in COVID-19 is characterized as a specific exudative widespread DAD accompanied with the involvement of the vascular bed of the lungs, massive capillary stasis, microthrombosis, and alveolar hemorrhage syndrome [32, 38–40].

Magro et al. [41] hypothesized a possible relationship between the new CoV infection and the activation of the complement system.

Su et al. [42] revealed the evidence that SARS-CoV-2 is capable of damaging the kidneys, causing acute kidney damage.

Stages of the pathological process in COVID-19 development. The division of the infectious process in COVID-19 into stages is still the subject of active discussion. However, researchers have already drawn some conclusions.

Chuchalin [35] suggested considering four phases of the clinical course of CoV infection.

1. The incubation period (5–9 days from disease onset) is manifested by adhesion and replication of the virus in the epithelium of the upper respiratory tract.

2. Prodromal period (up to 14 days from disease onset) is manifested by an inflammatory reaction, general symptoms (such as fever, ailment, rhinorrhea, swelling of the nasal mucosa, and moderate pain in the oropharyngeal region).

3. Peak of the disease (14–21 days from disease onset) is manifested by nonproductive cough, signs of respiratory discomfort, and damage to bronchioles and alveolocytes.

4. Complications include the formation of viral–bacterial pneumonia and ARDS.

Zayratyants [32] considered the classification of stages from the standpoint of morphology and distinguishes two phases.

1. Exudative phase (first 7–8 days, less often up to 14 days from disease onset).

2. Proliferative phase (7–8 days after disease onset).

Outcomes of COVID-19 pneumonia. Liu et al. [43] conducted a cohort study in China and analyzed the outcomes of COVID-19. The study included 1190 patients with COVID-19 of various stages and severity. Upon admission, the majority of the patients (1102, 92.6%) did not have severe disease. In 261 (22.7%) patients, the disease progressed after hospitalization (on average, within 12 days after hospital admission). Compared with non-progressive cases, a severe disease occurred in older patients (62 versus 55 years) and predominantly in men (60.1% versus 51.0%).

The role of concomitant diseases such as diabetes mellitus, hypertension, and chronic heart disease (chronic heart failure and coronary heart disease) in mortality was also demonstrated. Patients with comorbidities had lower survival rates and more severe symptoms. Survivors, compared with the deceased, had a lower average age (57 versus 69 years) and fewer comorbidities, including diabetes mellitus (12.2% versus 25.5%), hypertension (29.0% versus 41.8%), and chronic heart disease (6.3% versus 16.3%).

Liu et al. [43] emphasized the importance of diabetes mellitus as a risk factor of lethal outcomes, as the mortality rate is >11 times higher in patients with diabetes than in those without diabetes. Other significant independent risk factors of lethal outcomes were scores on the sequential/sepsis-related organ failure assessment (SOFA) upon admission, as well as leukopenia, lymphopenia, and increased D-dimer levels. Moreover, a higher SOFA score and lymphopenia on admission were predictors of higher disease severity in the hospital.

In July 2020, Karagiannidis et al. [44] published their study of the outcomes of 10,021 patients from 920 hospitals in Germany. The study revealed that most of the patients were >70 years old. The presence of at least one concomitant disease was a predictor of the need for artificial pulmonary ventilation (APV). Mortality rate up to 73% was recorded in patients who required simultaneous APV and hemodialysis. Mortality was high among patients on APV (53%), reaching 63% in patients aged 70–79 years and 72% in patients aged ≥80 years. According to Liu and Karagiannidis, these specific characteristics will help doctors clarify the progression and poor prognosis in patients with COVID-19.

According to Borczuk et al. [45], the median age of patients who died from COVID-19 was 73 years, and 69% of the deceased patients were men.

Pathomorphological characteristics. According to Zayratyants [32], characteristic morphological features are microangiopathy with pronounced lesions of the microvasculature, intense alveolar hemorrhage syndrome and various consequences of hypercoagulable syndrome, cytokine storm, hypoxia, and, possibly, and generalization of viral lesions.

The exudative stage (up to 7–8 days from disease onset) was characterized by intra-alveolar edema, desquamated epithelium in the lumen of

the alveoli, hyaline membranes of various thicknesses and lengths, desquamation of the alveolar and bronchiolar epithelium, proliferation and formation of symplasts from type 2 pneumocytes, destructive productive thrombovasculitis with the infiltration of the interalveolar septa, and multiple intrabronchial, intra-alveolar, and perivascular hemorrhages, causing pronounced alveolar hemorrhage syndrome, as well as the so-called megakaryocytic embolism characteristic of shock lungs, including septic shock.

In the proliferative stage (7–8 days after disease onset), alveolar damage was characterized by the accumulation of fibrin in the lumen of the alveoli, formation of granulations, confluent fields of obliterating bronchiolitis and organizing pneumonia, and areas of loose fibrosis with metaplastic epithelium. It is also characterized by pronounced interstitial inflammation with thickening and edema of the interalveolar septa, edema, and myxomatosis of the perivascular stroma [32].

The progression of microangiopathy and thrombosis of the microvasculature, branches of the pulmonary artery, and veins of various sizes in >20% of cases have been described. Moreover, a direct relationship and a higher mortality rate were established in patients with thrombosis than in patients without signs of thrombosis (risk of lethal outcomes is 74% higher) [46].

Unlike influenza, tracheobronchitis with bright hyperemia was not detected [32, 45]. The pronounced acute venous plethora is typical, and the majority (>60%) of the deceased patients had microangiopathy and disseminated intravascular coagulation with widespread hemorrhagic syndrome [32, 36, 38, 39].

The two-center study by Carsana et al. [47] analyzed a series of cases in northern Italy. In all cases, signs of exudative and proliferative phases of DAD were observed, which included the accumulation of capillaries, necrosis of the pneumocytes, formation of hyaline membranes, interstitial and intra-alveolar edema, hyperplasia of type 2 pneumocytes, squamous cell metaplasia with atypia, and thrombocytic-fibrin thrombi in small vessels (<1 mm). The inflammatory infiltrates noted in all cases mainly consisted of macrophages in the lumen of the alveoli and lymphocytes in the interstitium.

Histological examination of the main bronchi and branches of the bronchi revealed mild nonspecific changes, namely focal squamous cell metaplasia and mild transmural lymphocytic and monocytic infiltrates. Wall fibrosis was registered in 63% of the cases, as well as microcystic honeycombing (in 39% of the cases) with a focal distribution.

Carsana et al. emphasized that the prevalence and intensity of endothelial necrosis, an increase in the count of megakaryocytes in the alveolar capillaries, and widespread arteriolar fibrin-platelet thrombi are much more pronounced in COVID-19 cases than in typical DAD cases of other causes. These histopathological findings are confirmed by high (>10 times higher than the upper limit of the reference values) levels of D-dimer in the blood serum, which indicates intravital disseminated intravascular coagulation.

Zhang et al. [40] performed a postmortem transthoracic puncture biopsy of the lungs of a 72-year-old patient who died of respiratory failure associated with COVID-19. The lung tissue had organizing DAD with fibrinous exudate into the alveoli and chronic inflammatory infiltrates with interstitial fibrosis. Immunostaining specific for SARS-CoV-2 revealed viral particles in the alveolar epithelium, which were nearly not detected in the interstitium and vascular walls.

Li et al. [48] analyzed a three-dimensional histological reconstruction model obtained from lung tissue samples of patients who died from COVID-19. Their work emphasized the presence of megakaryocytes along with fibrin aggregates in small vessels of the lungs and viral cytopathic changes in pneumocytes.

Duarte-Neto et al. [49] performed 10 ultrasound-guided minimally invasive autopsies in patients with a positive test result for SARS-CoV-2 infection. Exudative proliferative DAD, cytopathic damage to the respiratory epithelium, and multiple alveolar megakaryocytes in the lung parenchyma have been described. Fibrinous microthrombi were revealed in alveolar arterioles, as well as in various vessels of other organs (glomeruli, testes, liver, and heart). Moreover, perivascular mononuclear skin infiltration was noted in eight cases, as well as in two cases of myositis and two cases of orchitis with diffuse changes in the endothelium of small vessels.

Bradley et al. described the results of 12 autopsies, including both complete and minimally invasive autopsies, of patients who died of COVID-19 [50]. Histological findings included acute and organizing DAD with type II reactive pneumocytes. Acute bronchiolitis and bronchopneumonia were also registered in two cases. Electron microscopy revealed viral particles in the cells of the lungs, trachea, kidneys, and colon. In addition to nonspecific chronic changes in various organs, the authors reported an acute lesion of the tubules in one case and periportal lymphocytic inflammation of the liver in two cases.

Grimes et al. [51] described the autopsy results of two patients who died from COVID-19. Pul-

Table 1. Comparison of bacterial pneumonia, influenza-associated pneumonia, and COVID-19

Symptom	Epidemiology		
	Bacterial pneumonia	Influenza-associated pneumonia	COVID-19
Source	Sick patient or objects of the environment	Sick patient	Sick patient
Pathogen	*S. pneumoniae*, *H. influenzae*, *Mycoplasma pneumoniae*, *S. aureus*, etc.	RNA-containing viruses of the *Orthomyxoviridae* family	RNA-containing SARS-CoV-2 virus of the *Coronaviridae* family
Target tissue	None	Epithelium of the upper respiratory tract and bronchioles, type 2 pneumocytes	Cells containing an ACE2 receptor
Mortality rate, %	0.6–8 [14]	0.4–48.7 [54]	0.53–0.82 [55]
Sign	Morphological characteristics		
	Bacterial pneumonia	Influenza-associated pneumonia	COVID-19
Bacteria	+	In secondary infection	In secondary infection
Viral particles	In secondary infection	In the epithelium of the upper respiratory tract	In tissues with an ACE2 receptor
Diffuse alveolar damage	–	+	+
Hyperemia, stasis	+	+	+
Hyaline membranes	In severe course	+	+
Alveolar edema	+	+	+
Interstitial edema	Rarely	+	+
Epithelial metaplasia	–	+	+
Leukocyte infiltration	+	+	+
Thrombosis of the microvasculature	Rarely	24% of cases	Severe

Note: RNA, ribonucleic acid; ACE2, angiotensin-converting enzyme type 2.

monary embolism was found in both cases, which causes occlusion of the right main pulmonary artery in one case and both main pulmonary arteries in the other. The finding was histologically confirmed, with both cases showing deep vein thrombosis of the lower extremities. Electron microscopy demonstrated viral inclusions in pneumocytes.

Suess and Hausmann [52] investigated the lethal outcomes of a patient with concomitant diseases (diabetes mellitus and hypertension). At autopsy, in addition to DAD and enlarged type II pneumocytes, signs of bacterial pneumonia in the lower lobes of the lungs, as well as the spread of infection into the heart tissue, were revealed. The disease development took a relatively short period (5 days), during which ARDS occurred, resulting in the lethal outcomes of the patients.

Borczuk et al. also reported the correlation of morbidity and mortality from COVID-19 with concomitant hypertension and diabetes mellitus [45]. Viral particles in pneumocytes were detected mainly in the first 2 weeks of the disease course, after which they were detected extremely rarely (in 3 of 23 patients studied within 5 weeks of the disease course) and locally. Scientists were interested in the fact that 11 of 68 patients had extensive lesions of the microvasculature of the lungs without the development of significant DAD. Thrombosis was registered more often in smaller-caliber vessels.

According to Calabrese et al. [53], the main pathomorphological finding is the acute fibrinous and organizing pneumonia, which, along with DAD, occurred in most cases. Microthrombosis of pulmonary vessels due to endotheliitis and the addition of bronchopneumonia were observed in more than half of the studies. Researchers consider widespread damage to the endothelium, leading to multiple organ damage to the microvasculature, as secondary, due to the body's immune response rather than the direct damaging effect of viral particles. This hypothesis is being actively discussed.

The results of a comparative analysis of bacterial pneumonia, influenza-associated pneumonia, and COVID-19 are summarized in Table 1.

CONCLUSIONS

1. When comparing the autopsy results of patients with COVID-19 and the data on pneumonia of a different etiology, a high morphological similarity with viral pneumonia in influenza was revealed.

2. A differential characteristic of SARS-CoV-2 is the presence of a specific pathway for entering cells through a tissue receptor that has an affinity for ACE2.

3. The combination of various stages of DAD, microthrombosis of the pulmonary arteries, and ability to induce endothelial dysfunction causing multiple organ failure appear to be the main identifying characteristics of the new CoV infection. These phenomena probably determine the severity of the disease course in COVID-19.

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