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MORPHOLOGICAL CHANGES IN PULMONARY VESSELS IN CORONAVIRUS INFECTION

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Abstract
It was found that the SARS-CoV-2 pathogen is characterized by causing varying degrees of changes in the endothelium and subendothelial layers of medium-sized blood vessels (muscular arteries). In particular, intermediate foci of edema and a sharp accumulation of acidic glycosaminoglycans were detected in the endothelial and subendothelial layers of muscular arteries. In order to detect these changes using histochemical methods, Alcian blue and Van Gieson stains were used. The bodies of people who died from COVID-19 infection were autopsied within 12 hours, and during the examination, immunohistochemical examination of the lung tissue of the corpse was performed, morphological changes in the tissues were studied and analyzed. Analysis of the study results showed that a high rate of vascular endothelial cell damage was characteristic of small precapillary and capillary blood vessels.

Keywords: SARS - CoV - 2, COVID - 19, pulmonary blood vessels, histochemical, immunohistochemical, endothelium, subendothelium, thrombus.

Introduction

During the COVID-19 pandemic, various types of information were collected in many countries, which prompted the creation of a concept of fundamental knowledge. During this pandemic, the mortality rate of the population from somatic diseases rose to third place (according to WHO data for June 2021). According to data provided by Russian scientists, in July and September 2021, patients with COVID-19 developed a sharp increase in myocardial infarction, acute renal failure, newly diagnosed diabetes mellitus, sinus thrombosis, and other complications [5]. In our country, among the complications after COVID-19, a high incidence of cerebral sinus thrombosis, thrombosis of the superior maxillary veins, aseptic necrosis of the femoral head, and other complications was noted. In the post-pandemic period, the number of deaths from complications of this disease worldwide increased by 2.1% compared to 2020 (154 million people), and in the USA and European countries, these cases were associated with complications of recurrent somatic diseases [1,2,5,7,11]. To date, a number of targeted studies have been conducted in many countries to assess morphological changes in blood vessels of patients who died from coronavirus infection. In this regard, studies aimed at explaining the role of anticoagulants in COVID-19 patients, especially outside the intensive care unit, concerns about blood clotting and COVID-19 vaccines, the risks and benefits of vaccination, cases of high blood clotting in COVID-19 infection, as well as studies aimed at assessing histochemical changes in pulmonary vessels, immunohistochemical features and morphometric parameters in pulmonary vessels of patients who died from thromboembolic complications of coronavirus infection are of particular scientific importance [3,8].

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Cytokine storms, i.e., pathological response of the immune system to the virus and the production of large amounts of cytokines, have been observed in some patients infected with coronavirus. The released cytokines not only kill the virus, but also damage cells in the body, including the endothelium. A sharp increase in cytokines in the blood causes the development of a diffuse inflammatory reaction. The virus damages the endothelium by damaging the interstitial tissue of the lungs and the outer adventitia layer of the capillary wall [4,7,10]. Through the damaged endothelium, the virus enters the bloodstream and spreads through the blood to all tissues and organs. As a result of damage to the endothelial layer of the blood vessel walls located in all organs and tissues, thrombosis and coagulopathy develop in the vascular space, which leads to circulatory disorders. Therefore, the lungs are also considered the epidemiological focus of the virus in COVID-19 [9,12,13]. To date, there is no complete information on how COVID-19 affects the heart and blood vessels. In addition, cardiovascular complications associated with COVID-19 remain a pressing issue today. In some patients, arterial thrombi have been observed, which directly affect the heart [9,13].

RESEARCH AIM

To study the morphological changes in the walls of pulmonary arteries during coronavirus infection from a histological, histochemical and immunohistochemical perspective.

MATERIALS AND METHODS

The study materials were prepared from lung tissue obtained from 35 patients who died of coronavirus infection during 2020-2021 at the Republican Center for Pathological Anatomy of the Ministry of Health of the Republic of Uzbekistan during autopsy. The obtained materials were fixed in a 10% formalin solution for 72 hours, and then dehydrated in alcohol of increasing concentration. Then, special blocks were prepared in paraffin and sections were taken from them. The sections were stained using hematoxylin eosin, Alcian blue and Van Gieson stains. For immunohistochemical examination, they were stained with IHC markers using automatic step-by-step staining on the Ventana equipment. The obtained data were morphologically checked and the obtained results were analyzed.

Results of the study and their discussion: the specific morphological changes in the wall of pulmonary arteries and small-caliber blood vessels were studied in the study. One of the unique aspects of the arterial blood vessel wall of the fine-caliber muscular type is that the intima layer is composed of endothelial and subendothelial layers, and normally the subendothelial layer contains neutral glycosaminoglycans, while the extracellular matrix consists of an orderly structure of the fourth type of collagen fibers. Sometimes, the projection and relief of these collagen fibers appear uniform in thickness on Van Gieson histochemical staining. It can be seen that the age-related changes are mainly in the 51-65-year-old age group, where the thickness of this layer does not appear in the projection of the same order as rough and uneven zigzag-like foci. In our study, the average age of those who died from COVID-19 was 53.8±7.56 years. This is an important point in interpreting our opinion without ignoring age-related changes in the vascular layers. Histologically, the muscle layer of the second and third order branches of the pulmonary trunk is very poorly developed, and the boundaries of the endothelial and subendothelial layers are usually not clearly

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distinguished from each other. In COVID-19 infection, these boundaries are clearly visible, leading to the accumulation of acidic glycosaminoglycans in the interstitial tissue and the formation of an acidic environment in the extracellular matrix.

This, in turn, is manifested by pathological processes in which a large amount of hyaluronic acid produced by fibroblasts accumulates, and as a result of the expansion of the vascular anastomosis and increased wall permeability in this area, interstitial edema and mucoid thickening develop (see Fig. 1). As a result, the transition of fibroblasts into a sharply active state increases the synthesis of fibrous structures, which leads to an increase in the synthesis of tropocollagen and collagen fibers from it in the subendothelial area. These changes can also be observed in other diseases, but one of the morphological features is that in COVID-19 infection, synchronous vasoparalytic and vasoconstrictive changes in the vessels are observed due to the blockade of the ACE-2 receptor in the vascular wall. As a result, these disorders are observed systemically in all organs [4,11]. Our research confirms the general changes characteristic of vascular wall damage.

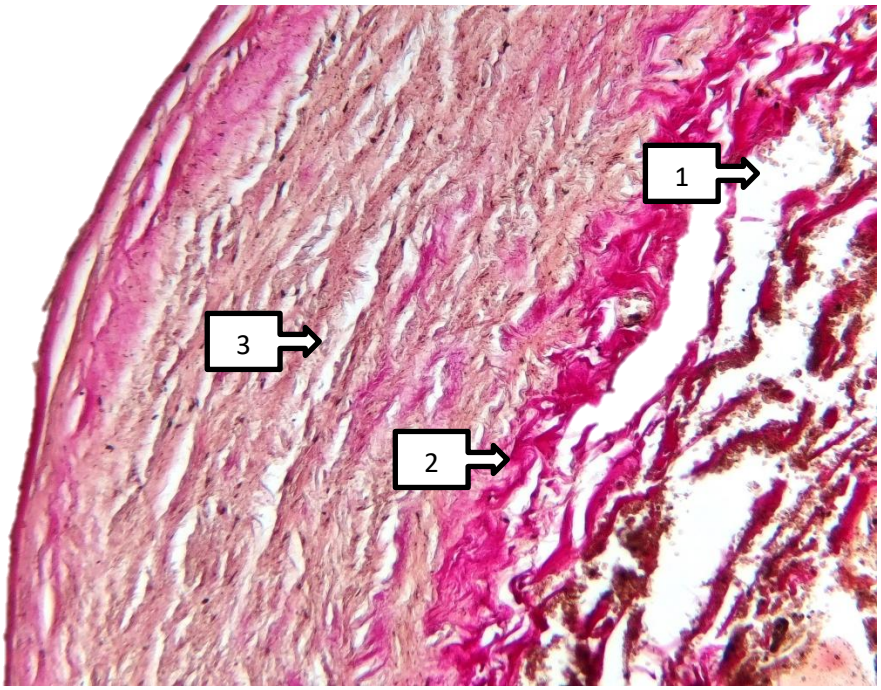

Fig. № 1. The patient is 41 years old. Pulmonary trunk. View of the wall of the second order pulmonary vein. Interstitial swellings and foci of desquamation are detected in the endothelial layer (1), sharply thickened foci of collagen fibers are detected in the border zone of the subendothelial layer (2), interstitial swellings and foci of collagen fibers have grown between them in the layer rich in elastic fibers (3). Paint Van Gieson. The size is 40x10.

In most cases, the accumulation of acidic mucopolysaccharides, which are considered Schiff-positive structures, indicates the destruction of fibrous structures due to the increased acidic environment in the foci of pronounced hypoxia. This morphological change is mainly manifested by the appearance of an edematous process in the extracellular matrix and the accumulation of monocytes in these areas (see Figure 2).

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Quaternary branches of the pulmonary artery and a sharp thickening of the wall of small-caliber vessels in hypertension, interstitial edema in the perimeter, the phenomenon of metachromasia, various degrees of hypertrophy of muscle cells, an increase in basophilic inclusions and Schiff-positive structures in the cytoplasm of myocytes, a sharp development of the hypoxia process, and the formation of a large number of coarse collagen fiber structures and destructive elastic-type fibers under the influence of an acidic environment. that it has changed, this has been confirmed in our research processes (see Figure 2).

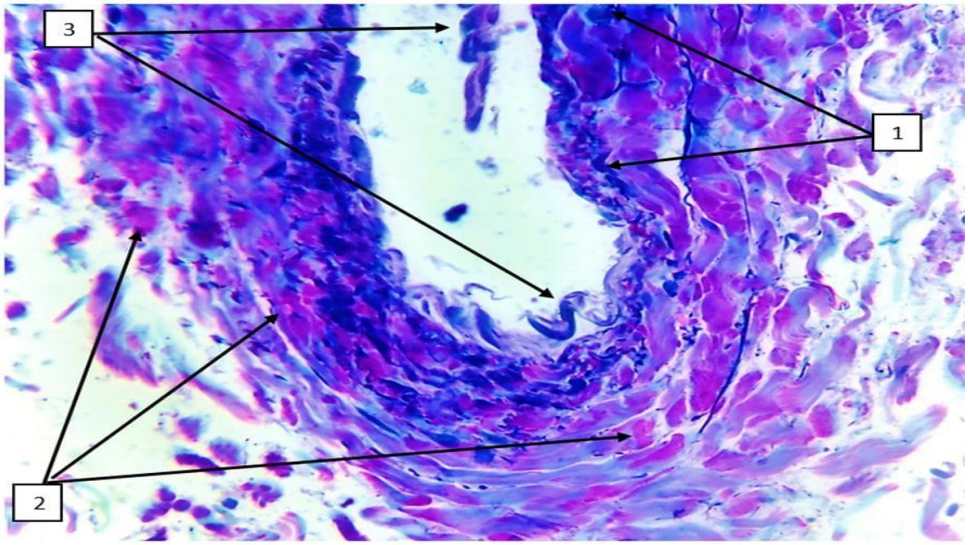

Fig.№ 2. A 56-year-old patient with hypertension and COVID-19. Fourth branch of the pulmonary artery. The vessel wall is thickened, hypertrophied myocytes in the muscle layers, a large number of SCHIFF-positive inclusions in their cytoplasm (1), accumulation of SCHIFF-positive structures in the interstitial tissue (2), the relief of the inner surface of the vessel is uneven, desquamation of endothelial cells, and platelet aggregation are detected (3). Stained with SCHIFF stain. Magnified 10x40 times.

COVID-19 infection, which developed against the background of hypertension, was characterized by the appearance of focal foci of inflammation, focal and multifocal desquamation of endothelial cells in the intima of small-caliber pulmonary arterioles (see Figure 2). This confirms the formation of intimal lesions and platelet aggregation in the intima and the development of the thrombotic process (see Figures 3-4).

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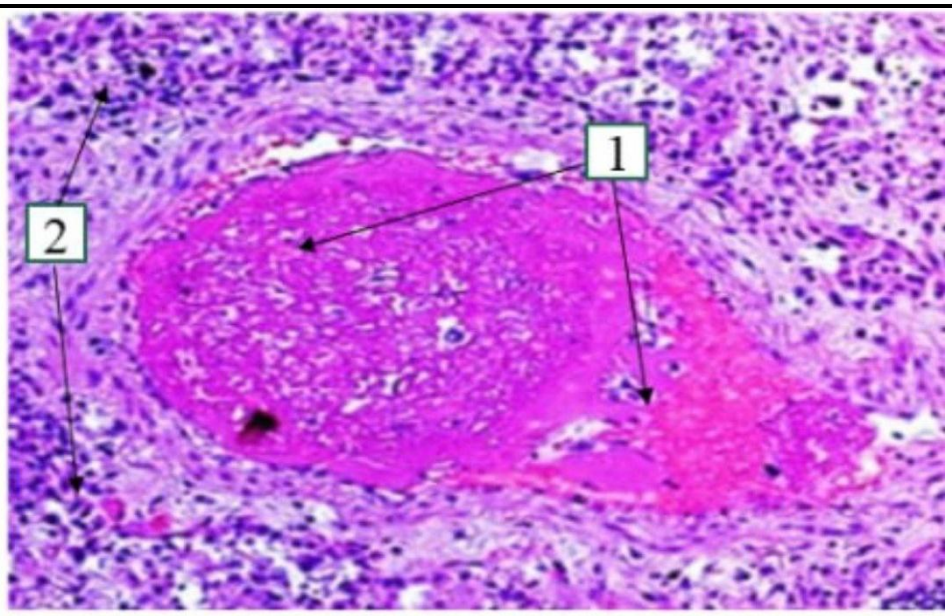

Fig.№ 3. Thrombus formed in the lumen of the tertiary branch of the pulmonary artery (1), infiltrative inflammation in the lung tissue (2). Stain G.E. Size 10x40.

It is precisely in COVID-19 infection that the endothelial membrane is rich in ACE-2 receptor, RLR receptor and DNA receptors, and as a result of the binding of these receptors and the simultaneous inhibition of the process, the active response on the surface of endothelial cells decreases, which leads to paralysis of the vascular wall and hydropic dystrophy and desquamation of endothelial cells, creating conditions for the formation of thrombus on the intravascular surface. In particular, focal formation of microthrombi is observed on the inner surface of precapillary arterioles, which leads to acute or chronic ischemia in organs in these areas (see Figures 3, 4, 5).

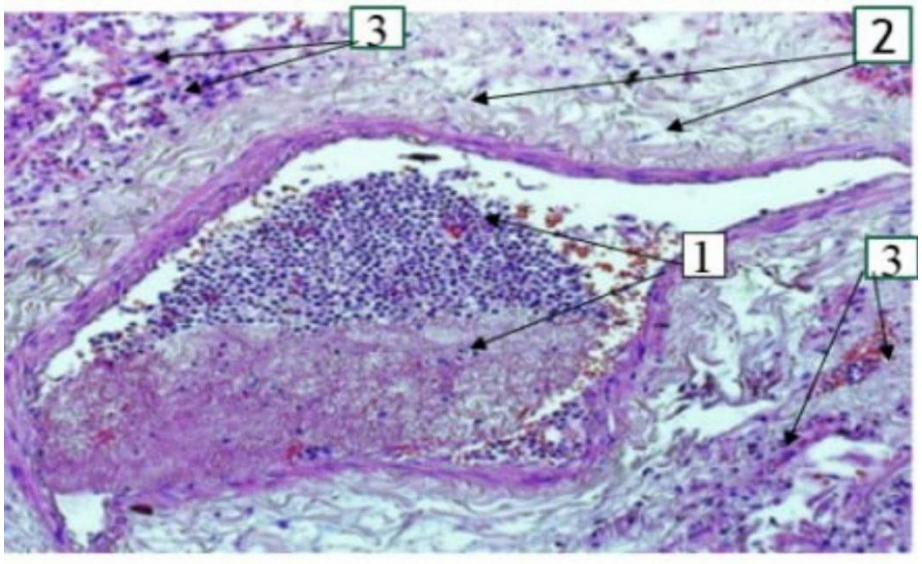

Fig .№ 4. Thrombus consisting of fibrin, leukocytes and erythrocytes in the cavity of the third branch of the pulmonary artery (1), perivascular swelling (2), infiltrative inflammation of lung tissue (3). Paint G.E. The size is 10x40.

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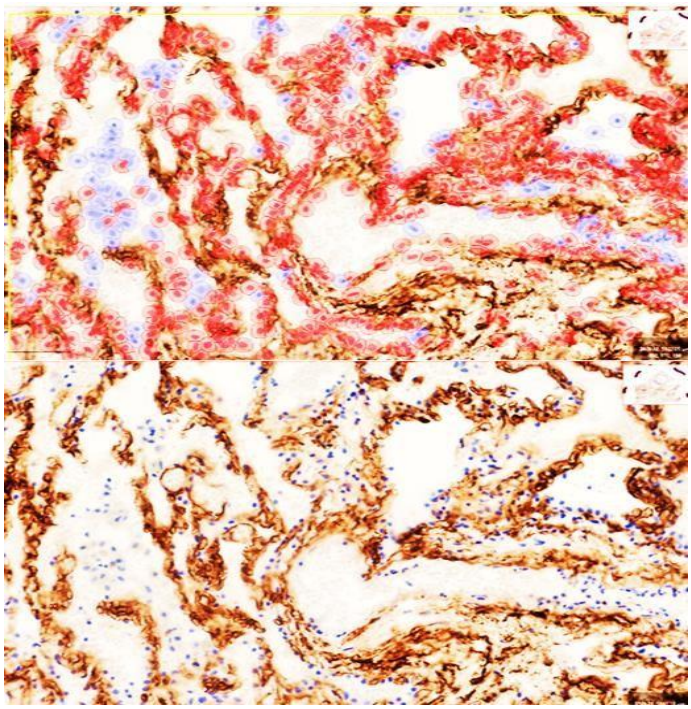
Based on the results of immunohistochemical examination, paraffin-embedded biopsy material with monoclonal antibodies was subjected to immunohistochemical examination using standard methods .



Number of cells detected	648
Negative expression	108
Positive expression	540
Positive expressed cells %	83,3%
Total area of positively expressed cells	2941,83 mkm^2
The total surface area of the tissue being measured	18355 mkm^2

Fig. № 5. Upper anterior lung tissue. Positive expression of the CD3 marker. Stained with a chromogenic dye. Magnified at 40x. Scanned and analyzed in QuPath-0.4.0.ink. The expressed cells are stained red.

The CD3 marker is expressed by binding to coreceptors on the membrane of T-killers, a subpopulation of T-lymphocytes. The high positive expression of the CD3 marker in COVID-19 infection confirms the parallel high positive expression index, which indicates a high concentration of viral etiology in inflammation, and also confirms the high rate of infection with COVID-19 in our study (see Figure 6)COVID-19 in our study (see Figure 6).

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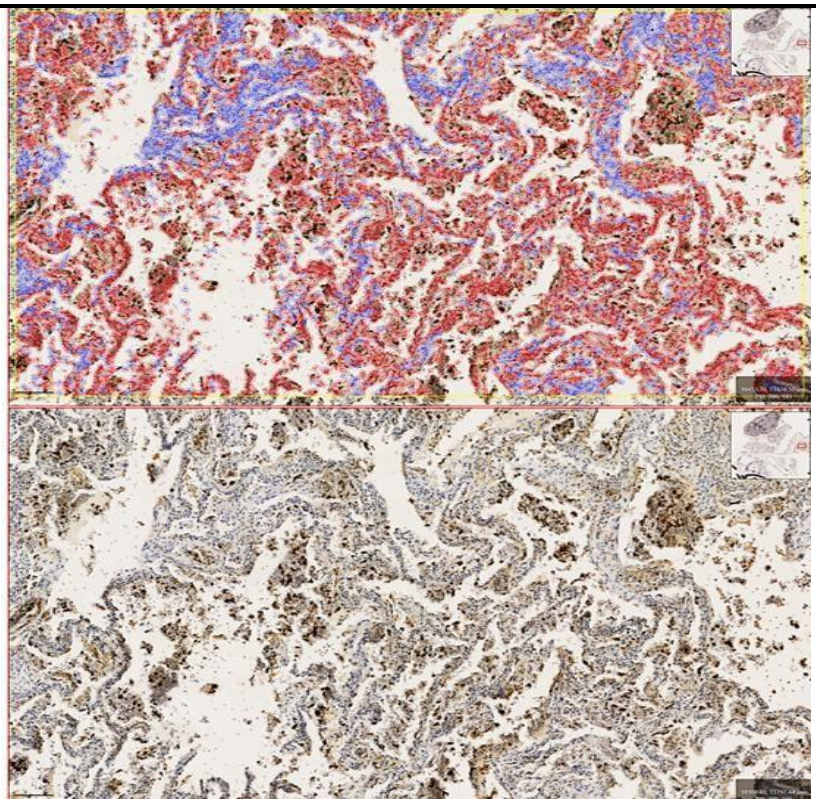

Number of cells detected	11475
Negative expression	2934
Positive expression	8541
Positive expressed cells %	74,43%
Total area of positively expressed cells	3466,68 mkm2
The total surface area of the tissue being measured	2463737 mkm2

Fig.№ 6. High positive expression of the CD 31 (PECAM-1) marker in lung tissue. Stained with Dab chromogenic dye. Magnified at 40x. Scanned and expression levels determined using QuPath-0.4.0.ink. Expressed cells are stained red.

High positive expression of the CD31 (PECAM-1) marker indicates the development of reangiogenesis in damaged capillaries and small blood vessels, and confirms that the inner surface of the vessel wall is most damaged in COVID-19, which leads to a high risk of developing microthrombi on the inner surface of the vessel, and thrombogenesis in medium and large vessels. This allows us to predict the expected thromboembolic complications in COVID-19. Such indicators serve as one of the main criteria for determining the economic and social effectiveness of our research work (see Fig. 7).

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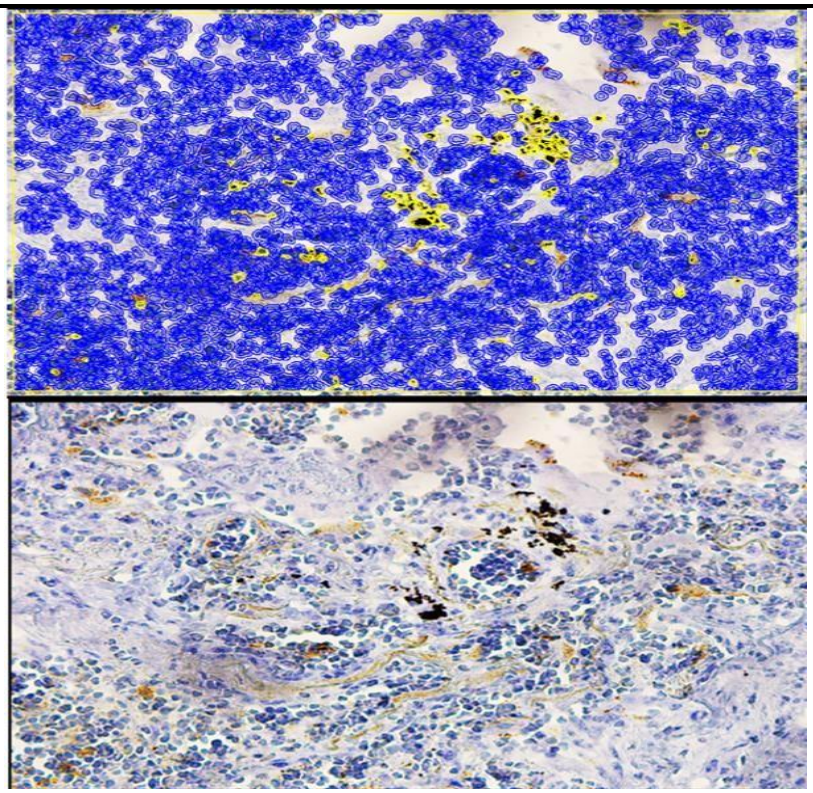

Number of cells detected	2991
Negative expression	2885
Positive expression	106
Positive expressed cells %	3,54%
Total area of positively expressed cells	0,0001 mkm^2
The total surface area of the tissue being measured	3888578 mkm^2

Fig.№ 7. Lung tissue. Low positive expression of VEGFA-1 marker. Scanned and expressed using QuPath- 0.4.0.ink. program. Expressed cells are stained yellow. Stained with Dab chromogenic dye. Magnified at 40x.

According to the analysis of the data obtained by staining with the VEGFA-1 marker in our study, the low positive expression of the VEGFA-1 marker indicates that COVID-19 infection sharply inhibits any angiogenic factors, which means that the mesenchymal cells are not at a concentration that can stimulate endothelial growth factor through direct damage to the walls of small-caliber vessels and capillaries (see Figure 8). In addition, this process indicates the completion of reparative regeneration of damaged tissues and blood vessels in the form of substitution or complete scarring and sclerosis.

CONCLUSIONS

1. In COVID-19, it was found that a large number of Schiff-positive structures in the pulmonary artery wall, interstitial edema, changes in the intravascular relief, focal damage to the folds of the endothelial surface and the formation of thrombi in these areas, lead to focal damage.

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2. In COVID-19, it was found that collagen fibers in the pulmonary artery wall, changes in the intravascular relief and disruption of the smoothness of the inner surface of the vessel, which leads to the formation of thrombi on the endothelial surface, are formed to varying degrees.
3. Clinically and morphologically, arterial vessel deformation, the formation of thrombi in vascular spaces, acute thrombosis and vascular occlusion lead to the formation of infarct foci.
4. In COVID-19 infection, the accumulation of CD3 lymphocytes in the foci of inflammation is precisely around the perivascular and intravascular subendothelial tissue, which confirms the severity of the inflammatory process in these areas, and the high positive expression of the CD3 marker in most cases.
5. In addition to indicating the development of damaged capillaries and small blood vessels in the process of reangiogenesis as a result of the high positive expression of the CD31 (PECAM-1) marker, the low positive expression of the vascular endothelial growth factor VGEF-1 confirms the high probability of damage to the inner surface of the vessel wall in COVID-19, the development of microthrombi on the inner surface of the vessel, and the development of thrombogenesis in medium and large vessels.

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