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CLINICAL AND MORPHOLOGICAL CHARACTERISTICS OF COVID-19 ASSOCIATED MYOCARDITIS

The article is devoted to the actual problem in the case of ongoing COVID-19 pandemic – the clinical and morphological characteristics of COVID-19 associated myocarditis in conditions of non-widespread of this topic.

The aim of the study is to study the clinical and morphological features of COVID-19 associated heart damage in deceased patients. The study included data from medical cards of inpatients of Almaty City cardiological center, as well as postmortem data of 12 patients (9 men and 3 women, average of age 65,6 ± 13,8, 51–80 years), dead patients with a diagnosis of atherosclerosis-associated diseases. Pathological anatomical autopsy was performed at the Central Pathological Anatomical Department of Federal Health Institution "Central Medical and Sanitary Unit No. 1 of the Federal Medical and Biological Agency Hospital №1 Russia. Extrapolating data from the pathomorphological study of deceased patients, who had a history of coronavirus infection and died from circulatory system diseases, on autopsy it was found that SARS-Cov-2 infection led to the development of subacute/chronic myocarditis. Its clinical manifestations develop within 4-6 months or more than a year after acute COVID-19 in the form of myocardial infarction or progressive heart failure. The researchers also emphasize the extreme importance of performing autopsy studies of any nosology in combination with COVID-19, for subsequent clinical and morphological analysis, which provide invaluable opportunities to summarize each morphological manifestation of this infection to be further compared to clinical manifestations.

Thus, at present, any unclear myocardial dysfunction requires serodiagnosis of a new coronavirus infection. SARS-Cov-2 infection can cause chronic nonbacterial lymphocytic thromboendocarditis with an autoimmune mechanism; as well as its combination with lymphocytic myocarditis. Research in this field still needs to be continued.

Key words: coronavirus infection, autopsy, COVID-19, myocarditis, pathological signs of myocarditis, histology, alveolar damage with desquamation.

Introduction

Structural changes in the myocardium during coronavirus infection have been described by many authors. According to researchers from Wuhan myocardial damage was diagnosed in 5 cases, out of 41 patients [1]. COVID-19 is associated with numerous cardiovascular pathologies, including myocarditis, acute myocardial infarction, endo- and pericarditis, small-focal cardiosclerosis, and cardiomyopathy [2]. At the same time, this period after acute COVID-19 vary from several months to six months or even more. [2-4]. Cardiovascular manifestation in COVID-19 is diverse: acute myocardial infarction, myocarditis, stress-induced cardiomyopathy, non-ischemic cardiomyopathy, coronary spasm [5-7]. The progression of cardiac symptoms in some patients became the basis for the study of the level of immunoglobulins G (IgG) to SARS-Cov-2 and the retrospective diagnosis of this infection.

There appeared a cohort of newly diagnosed patients, presenting dilatation of all cavities of the heart and a decreased ejection fraction less than 50%, refractory to standard therapy for chronic heart failure, with clean coronary vessels according to coronary angiography [7].

Cardiomyopathy in COVID-19 has been described in a limited number of works and, according to the reference materials it occurs in 33% of cases [8-10]. Lymphocytic pericarditis and endocarditis may develop in association with COVID-19-associated lymphocytic myocarditis. The endocardium is often thickened, sclerosed, with residual effects of endocarditis (lymphoid infiltrates) [11,12].

Our observations of the treatment of cardiological patients at the city cardiological center demonstrate that more than 50% of patients got sick with COVID-19 and suffered deterioration of their condition (blood pressure drops, weakness, increased dyspnea, palpitations, rhythm

disturbances, a significant decrease in exercise tolerance and etc.).

After a scientific and practical conference about the results of COVID-19 in 2021, where Dr. Bukeshov M.K. presented autopsy data of patients with COVID-associated myocarditis, we have an idea for a joint study of heart lesions after a coronavirus infection and identification of clinical and laboratory data from patients with autopsy data.

Purpose of the study: Study of clinical and morphological features of COVID-19 associated heart diseases in deceased patients.

Materials and Methods

The study included data from medical cards of inpatients of Almaty City Cardiological Center, as well as postmortem data of 12 patients (9 men and 3 women, average of age 65,6±13,8, 51–80 years), deceased patients were diagnosed with atherosclerosis-associated diseases. According to the pathoanatomical autopsy conclusion all of them had been diagnosed with "post-covid myocarditis". Pathological anatomical autopsy was performed at the Central Pathological Anatomical Department of Federal Health Institution "Central Medical and Sanitary Unit No. 1 of the Federal Medical and Biological Agency of Russia, Hospital №1.The entry criteria included presence or noticeable progression of symptoms of heart damage (rhythm disturbances, myocardial infarction, progression of heart failure), with a history of coronavirus infection, verified serologically or PCR-positive for COVID-19 autopsy biomaterial, in the presence of morphological criteria for myocarditis of autopsy materials according to 2013 ESC guidelines/or Dallas criteria for myocarditis. The exclusion criteria were hemodynamically significant (more than 50%) including coronary artery stenoses (for patients older than 40 years), acquired heart defects, hypertensive heart (hypertrophy more than 14 mm), diffuse connective tissue diseases, systemic vasculitis, sarcoidosis, dilated cardiomyopathy.

Results and Discussion

Lifetime diagnosis of COVID-19 was confirmed by positive PCR results in two cases and the subsequent appearance and persistence of anti-SARS-Cov-2 IgG in all patients according to autopsy data. At the time of admission to the clinic, the PCR test was negative in all patients. The low percentage of positive nasopharyngeal smears is due to their late performance or their failure (no suspicion of COVID-19). COVID-19 was suspected and diagnosed retrospectively in 3 patients and all of them had COVID-19 in their history. There were no hospitalizations for COVID-19 in any case.

In the morphological part of the study there were used data from autopsy materials of those who died in the hospital, who stayed no more than 2-3 days. All those who died with a relatively moderate clinical severity of the condition had an unexpectedly fast rate of death, a sudden development of bradycardia with a sharp transition to asystole with respiratory depression, with a stable high saturation in the previous state. The clinical course of all autopsy cases was not expected to show such rapid lethal outcomes, which attracted the special attention of researchers in the first place. The data of the medical record of clinical cases and the results of autopsy in a comparative analysis also corresponded to the cardiac mechanism of death, which was characterized by a bright short cardiac thanatogenesis, in autopsy cases it was unambiguously confirmed by the results of macro- and microscopic studies of pathological processes in various organs, especially in the myocardium. These data allowed considering that the main pathological substrates for this study were myocardial lesions during or after COVID-19. In addition, autopsy clinical findings were also summed up individually in the context of polyorgan autopsy morphological changes, which made it possible to evaluate the previous or persistent COVID morphology in various organs, although not all had a previous respiratory history.

For the clinical part, each case in this study was analyzed by stationary data based on clinical, laboratory and instrumental observations with further differential assessment in terms of traditional pathophysiological presentations currently existing in COVID-19 in combination with various comorbid diseases.

Bilateral viral pneumonia was diagnosed in 3 out of 12 patients who underwent computed tomography (CT) of the chest: in one case, the volume of the lesion did not exceed 25% (CT-1), in two patients it was 25–50% (CT-2). These patients developed grade 1 respiratory insufficiency; however, there was no need for non-invasive or invasive ventilation.

Troponin levels were not assessed. The cause of the last hospitalization during which death occurred: 10 of the 12 deceased had acute coronary syndrome, which in 5 patients was transformed into type 2 myocardial infarction, in 1 – into an aneurysm rupture, in 2 – into unstable angina, in 2 – cardiomyopathy with decompensation of CHF (1- dilated cardiomyopathy and 1- ischemic cardiomyopathy). One patient was admitted with a clinic of hypertensive crisis and the development of stroke, and only 1 patient with a clinic of community-acquired pneumonia.

All patients had echocardiographic signs of left ventricular systolic dysfunction in the form of decreased ejection fraction less than 50%, which were detected in vivo during hospitalization. There were also cardiac symptoms and symptoms of heart failure during the last months before hospitalization (from 1 to 4 months), which gradually increased.

Concomitant diseases. The average body mass index was 26.4±5.6 kg/m2, obesity of the 1st degree was in 1 (8.3%), the 2nd degree in 1 (8.3%), overweight in 4 patients (33.3%), 6 patients (50%) had normal weight.

Two patients had diabetes mellitus type 2, arterial hypertension of the 2nd or 3rd degree – 8 patients, two patients had a history of stroke, each patient in the anamnesis had autoimmune thyroiditis, bronchial asthma, cancer of the uterine body, CKD stage 4, respectively. Lactate more than 2 mEq/l was observed in 10 of 12 patients, which probably indicates increased aerobic and anaerobic glycolysis against the background of a septic state in deceased patients. None of the patients was diagnosed with post-covid myocarditis during their lifetime.

Pathomorphologically, in general in lungs, all the deceased had a similar picture, macroscopically, the lung tissue was anaemic, diffusely compacted, in some cases organized thrombus in the lumen of the segmental arteries, separate scattered subsegmental atelectasis, focal interlobar fresh fibrinous transparent adhesions. They depend on the period of recent covid pneumonia walking through severe (Figure 1).

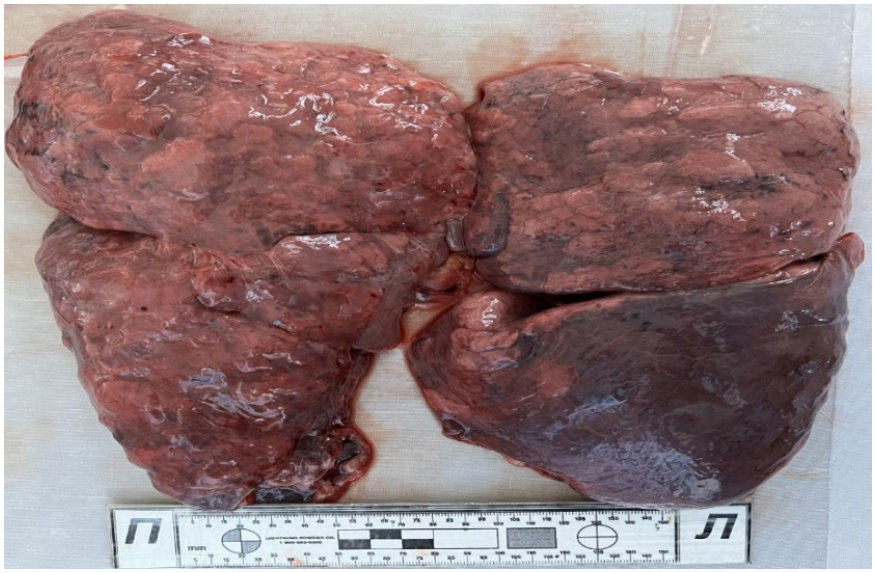

Figure 1 – Macroscopic changes in lungs after COVID-19,
lungs are compacted, focal atelectasis, interlobar fresh fibrin adhesions

Histologically, the architectonics of lungs is mainly represented by edema of alveolar walls with lymphoplasmacytic infiltration in the background of which there is alveolar damage with desquamation in their lumen, individual alveolocytes are hypertrophied and necrotic. There is observed the formation of multinuclear symplasts (Figure 2). Along the contours of the alveolar walls, there are fragments of hyaline membranes with organized and severe thrombosis of small arteries and arterioles; there are often found lymphocytic cell infiltrations of vessel walls. In some cases, in the background of widespread atelectasis, there are multiple focal sclerosis and fibrosis of alveolar walls, with deformation and the formation of large thick-walled newly formed alveolar lumens with a moderate accumulation of desquamated alveolocytes. Perivascular sclerosis, pronounced edema with disintegration of the walls of arteries and arterioles, thrombi are predominantly erythrocytic. Large veins are empty, the walls with signs of paralysis, the walls of small veins are pronouncedly edematous with plasma impregnation, their stasis is in the lumen. The capillaries of the alveolar walls are sharply dilated, mostly desolate. In the lumen of individual alveoli, along with alveolar desquamation scattered individual intraalveolar edema was observed in some places, in other fields of vision, an accumulation of reticular fibrin, in the background of which focal emphysema was observed in a small area.

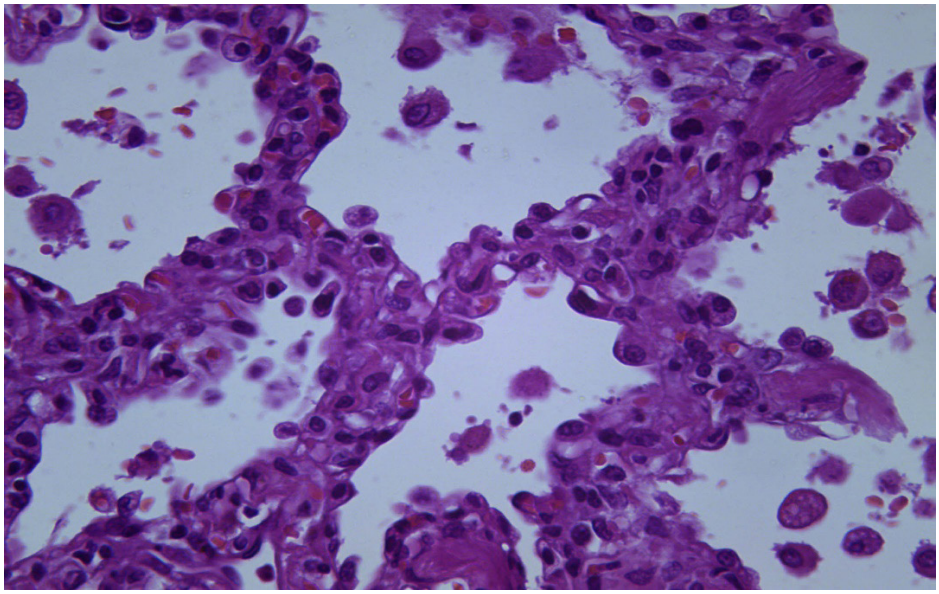

Figure 2 – Alveolar walls are edematous, infiltrated with lymphocytes and plasmocytes, desquamation of alveolocytes, interstitial pneumonia in COVID-19. S tained with hematoxylin and eosin

In the large bronchi, the peribronchial zone is moderately sclerosed, edematous, disintegrated, the muscle component is pronounced edematous, foci of distinct myocytolysis, swelling of the submucosal layer with pronounced plethora with cellular infiltration, subsegmental cytolysis is noted in the peribronchial glands, part of the respiratory epithelium is completely destructed, part is necrotic, in smaller bronchial tubes, there is a spasm of the walls, swelling of the submucosa with plasma impregnation, the respiratory epithelium in them is focally destructed and necrotic.

In the pathoanatomical conclusion, all deceased patients had polysegmental interstitial pneumonia, focal fibrosis of varying severity, vasculitis, mainly arterioles. These data are also confirmed by other authors [11, 13].

The pathomorphological picture of changes in the heart of the deceased made it possible to identify the following myocarditis-like changes: in the pericardium there was serous-hemorrhagic exudate, the volume of which is from 0.2-0.5 ml to 15.0-20.0 ml, macroscopically in the lumen of the aorta and in the cavities of the heart, anemia, color and consistency of myocardium remained unchanged except for infarct variants (Figure 3.). Histologically, stromal inflammation, hypertrophy of cardiomyocytes, large and small-focal scattered non-coronary necrosis, predominantly a separate, single, strip-like form, in rare cases, in places they were confluent, without a perifocal cellular reaction, necrotic foci, sometimes in varying degrees of severity, due to the onset of fibrosis of the necrosis zone with single lymphocytes, acquiring a reticulated appearance, which may indicate the duration of the process. Moderately pronounced arterioarteriolosclerosis, pronounced edema of the walls of large arteries with fibrillation, thrombosis was observed in small arteries. Severe spasm of arterioles with lymphoplasmacytic infiltrates, endothelium swollen nuclei hypertrophied. Congestion of veins, stasis with sludge. Mostly in the stroma and interfascicular space, lymphocytic and plasmacytic infiltrates were observed, sometimes with an admixture of leukocytes, in the background of fibrin exudation.

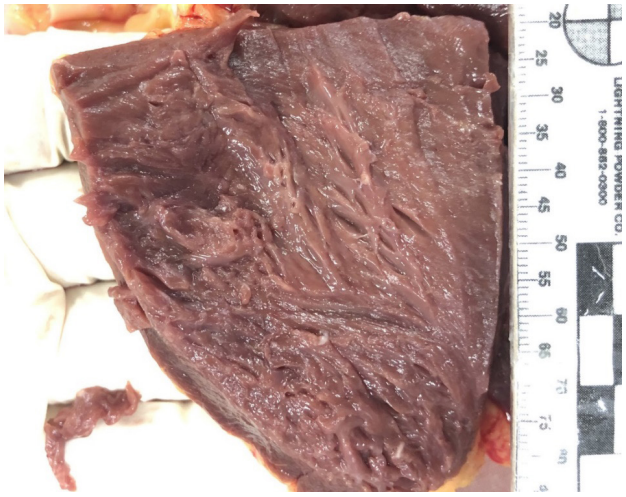

Figure 3 – Macroscopic myocardium of the anterior wall of the left ventricle in COVID-19 associated serous myocarditis

Cellular infiltration is more pronounced in areas with plasma impregnation (Figure 4), in places with necrosis and fibrillation of the vascular walls, mostly of small caliber, sometimes small hemorrhages and deposits of siderophages are noted in the area of cellular infiltration.

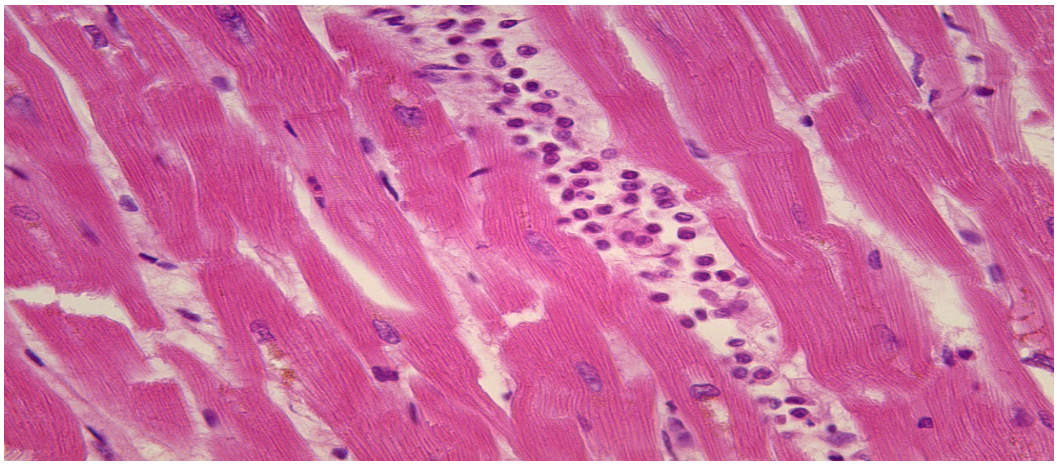

Figure 4 – Myocardial stroma with exudative impregnation, in the background of which lymphocytic and plasmacytic infiltration in the myocardium in COVID-19 associated serous myocarditis. Stained with hematoxylin and eosin

In some cases, subsegmental small foci of myocytolysis were noted, occupying the entire field of view at low magnification. In the background of the above processes, fragmentation, dissociation and wave-like deformations, foci of lumpy decay and occasionally occurring wave-like deformations were traced. In the background of pronounced hypertrophy of the nuclei of cardiomyocytes, in the perinuclear spaces there was non-pronounced strip-like accumulation of small droplets of lipofuscin granules. These macro and microscopic pictures made it possible to identify the following in deceased patients: serous myocarditis. In 7 cases there were observed small-focal non-coronary necroses, which were diffuse and rarely confluent, as well as type II infarcts. Myocardial hypertrophy was detected in all patients.

Conclusion

Extrapolating data from a pathomorphological study of deceased patients who had a history of coronavirus infection and who died of diseases of the circulatory system, on autopsy it was found that SARS-Cov-2 infection led to the development of subacute/chronic myocarditis.

Its clinical manifestations develop within 4-6 months or more than a year after acute COVID-19 in the form of a clinic of myocardial infarction or progressive heart failure. That is, post-covid myocarditis manifested itself in two main clinical forms – infarction-like and decompensation (systolic dysfunction with or without chamber dilatation, as well as type 2 infarcts when comparing EchoCG and autopsy data). Obviously, the main mechanisms of post-covid myocarditis are the long-term persistence of SARS-Cov-2 in the myocardium (cardiomyocytes, endothelium, macrophages) in some patients, combined with high immune activity (high titers of anticardiac antibodies in patients).

Thus, at present, any unclear myocardial dysfunction requires serodiagnosis of a new coronavirus infection. SARS-Cov-2 infection can cause chronic nonbacterial lymphocytic thromboendocarditis with an autoimmune mechanism, as well as its combination with lymphocytic myocarditis. In the treatment of postcovid myoendocarditis, clinically occurring with symptoms of CHF refractory the possibility of using corticosteroids and anticoagulants should be considered along wih treatment and dilatation of the heart cavities or an ACS clinic. Research in this direction needs to be continued.

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