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МИОКАРДИТ, АССОЦИИРОВАННЫЙ С COVID-19: КЛИНИЧЕСКИЙ РАЗБОР СЛУЧАЯ С ЛЕТАЛЬНЫМ ИСХОДОМ

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Myocarditis Associated with COVID-19: Review of a Fatal Case Report

Резюме

По состоянию на февраль 2024 года вирусом SARS-CoV-2 было инфицировано более 774 миллионов человек во всем мире и погибло от COVID-19 более 7 миллионов человек. С начала пандемии появилось множество сообщений и исследований о вовлечении в поражение вирусом SARS-CoV-2 параллельно с дыхательной системой и сердечно-сосудистой, включая повреждение миокарда, эндотелиальную дисфункцию, острые коронарные синдромы, аритмии, миокардит, тромбоэмболию, сердечную недостаточность, гипотонию, кардиогенный шок и даже остановку сердца. Кроме того, симптомная инфекция COVID-19 с тяжелым течением чаще встречается у коморбидных пациентов при наличии в анамнезе гипертонии, сахарного диабета, ожирения, онкологических заболеваний или хронической обструктивной болезни легких. Согласно последним литературным данным возникновение миокардита, ассоциированного с новой коронавирусной инфекцией, чаще наблюдается у лиц мужского пола молодого возраста и сопряжено с тяжелым или даже летальным прогнозом, что обуславливает актуальность детального изучения патогенетических механизмов и терапевтических возможностей профилактики развития миокардиального повреждения, купирования основных симптомов заболевания и предотвращения неблагоприятного прогноза. На сегодняшний день существуют также исследования, указывающие на то, что острый миокардит может являться осложнением не только самой инфекции в остром периоде или отсрочено, но даже одним из тяжелых поствакцинальных против SARS-CoV-2 осложнений. Целью нашего исследования является анализ летального случая острого инфекционного миокардита, осложнившего течение новой коронавирусной инфекции. Был проведен ретроспективный анализ истории болезни пациента с окончательным диагнозом острый коронавирусный миокардит, развившийся на фоне синдрома некомпактного миокарда левого желудочка.

Ключевые слова: *миокардит, COVID-19, SARS-CoV-2, сердечно-сосудистые заболевания, некомпактная кардиомиопатия, клинический случай, пневмония*

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Abstract

To date more than 774 million people worldwide were infected with the SARS-CoV-2 virus (data for February 2024), and approximately 7 million people have already died from COVID-19. Since the beginning of the COVID-19 pandemic, there have been many reports and studies

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on damage involvement of the SARS-CoV-2 virus not only the respiratory but cardiovascular system as well, including myocardial damage, endothelial dysfunction, acute coronary syndromes, arrhythmias, myocarditis, thromboembolism, heart failure, hypotension, cardiogenic shock and even cardiac arrest. In addition, symptomatic COVID-19 infection with a severe course is more common in comorbid patients with a history of hypertension, diabetes, obesity, cancer or chronic obstructive pulmonary disease. According to the latest literature data, the occurrence of myocarditis associated with a new coronavirus infection is more often observed in young males and is associated with a severe or even fatal prognosis, which determines the relevance of a detailed study of the pathogenetic mechanisms and therapeutic possibilities for myocardial damage prophylaxis, relieving the main disease symptoms and unfavorable prognosis prevention. To date, there are also studies indicating that acute myocarditis could be a complication not only of the infection itself, but even one of the severe post-vaccination against SARS-CoV-2complications. The purpose of this study is to research the lethal clinical case of acute infectious myocarditis complicated the course of a new coronavirus infection. A retrospective analysis of the patient's medical history with the final diagnosis: acute coronaviral myocarditis against the background of non-compact left ventricle myocardium was carried out.

Key words: *Myocarditis, COVID-19, SARS-CoV-2, cardiovascular diseases, noncompaction cardiomyopathy, clinical case, pneumonia*

Conflict of interests

The authors declare no conflict of interests

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ACE2 — angiotensine converting enzyme 2, COVID-19 — CoronaVirus Disease 2019, Ig — immunoglobulin, NT-proBNP — N-terminal prohormone of brain natriuretic peptide, WR — Wassermann reaction, SARS-CoV-2 — severe acute respiratory syndrome-related coronavirus 2, SpO_2 — peripheral oxygen saturation, AVF — atrioventricular foramen, BP — blood pressure, AB — antibodies, DCMP — dilated cardiomyopathy, ELISA — enzyme-linked immunosorbent assay, LVEDD — left ventricle end-diastolic dimension, LVEDV — left ventricular end-diastolic volume, COI — cutoff index, LVESD — left ventricle end-sistolic dimension, chest CT — computed tomography of thoracic organs, LV — left ventricle, LA — left atrium, ATV — anterior tibial vein, IVS — interventricular septum, IU — international units, MSCT — multispiral computed tomography, NCCMP — noncompact cardiomyopathy, NMRC — National Medical Research Center, ACVE — acute cerebrovascular event, RV — right ventricle, RA — right atrium, PCR — polymerase chain reaction, PET — positron emission tomography, RVC — Regional Vascular Center, CVMR — cardiovascular magnetic resonance, CI — cardiac insufficiency, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein, LVPWT — left ventricular posterior wall thickness, IVST — interventricular septum thickness, LVWT — left ventricular wall thickness, EF — ejection fraction, FC — functional class, daily monitoring of ECG — 24-hour Holter monitoring, RR — respiratory rate, HR — heart rate, ECG — electrocardiography, EMB — endomyocardial biopsy, CEA — cardiac electrical axis, echoCG — echocardiography

Introduction

Myocarditis is a multifactorial disease; however, according to recent overviews, the main cause of myocarditis is viruses. At the moment, highly relevant are reports on coronavirus-associated myocarditis, caused by vaccination or past coronavirus disease 2019 (COVID-19) [1]. Currently, there are at least three pathogenic mechanisms of virus-induced myocardial damage mediated by severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2). First, marked systemic inflammatory response causes a significant increase in the levels of circulating pro-inflammatory cytokines, which can lead to cardiac myocyte dysfunction by direct inhibition of their contractile ability, and, thus, to depression of the myocardial function, a condition, which was previously described in patients with sepsis [2]. Second, expression of angiotensine converting enzyme 2 (ACE2) receptor in the myocardium can contribute to its direct infection, attraction of immune cells and development of infectious myocarditis [3, 4]. Third, effect of SARS-CoV-2 on the microcirculation by affecting ACE2 receptors can cause microvascular dysfunction and tissue ischaemia, facilitated by platelet hyperaggregation and hypercoagulation, which result in cardiac insufficiency because of dysfunctional ventricles, and/or arrhythmias [5]. The possibility of drug-induced myocardium damage cannot be ruled out when taking cardiotoxic medications to treat cardiac insufficiency (CI) and novel coronavirus infection (for instance, hydrochlorothiazide, furosemide, methyldopa, azithromycin, penicillins, ampicillin, sulfanilamides, tetracycline). Usually, this myocardial damage develops to eosinophilic myocarditis [6].

Initial diagnosis is based on clinical data, laboratory test results, electrocardiography (ECG) and imaging examination, such as echocardiography (echoCG), FDG-enhanced positron emission tomography (PET) or cardiovascular magnetic resonance (CVMR). For diagnosis verification, analysis of available test results is usually not sufficient, endomyocardial biopsy (EMB) is required; it is an invasive gold standard for diagnosis of inflammatory diseases of the myocardium and its verification using histological, immunological and immunohistochemical criteria, especially if giant cell myocarditis is suspected or when the clinical representation of the disease includes cardiovascular shock with rapid hemodynamic disorders [7]. Taking into account challenges in diagnosis of COVID-19-associated

myocarditis, especially performance of EMB, it is currently impossible to reliably estimate the incidence of this complication. According to the CORONA study (Germany) in patients hospitalised with the novel coronavirus infection, the risk of death is almost 5 times higher if clinical signs of acute cardiovascular events are involved [8]. Poor prognosis warrants the importance of timely forecasting and prevention of cardiovascular complications of COVID-19, their early identification and thorough clinical follow-up of this population. Of interest is the study of a fatal case of severe acute infectious myocarditis caused by the novel coronavirus infection.

Clinical Study

Patient P., male, 35 years old, was admitted on January 3, 2022 to the Cardiology Unit, complaining of feeling faint, shortness of breath during minor physical exercise, which aggravated in horizontal position.

Medical history. From December 14, 2021 to December 24, 2021, the patient was undergoing inpatient treatment at the COVID centre of the State Budgetary Healthcare Institution of the Republic of Crimea Simpheropol State Clinical Hospital No. 7 with the moderate novel coronavirus infection (COVID-19); the diagnosis was verified with polymerase chain reaction (PCR) and chest multispiral computed tomography (MSCT). The therapy included antivirals (favipiravir according to the schedule, 10 days), anti-inflammatory drugs (dexamethasone 16 mg/day), anticoagulants (heparin 10,000 IU/day, then rivaroxaban 20 mg/day), as well as standard therapy for chronic cardiac failure (torasemide 5 mg/day, verospiron 25 mg/day, bisoprolol 2.5 mg/day). During hospitalisation, the patient underwent echocardiography (*echoCG) (December 21, 2021,* which revealed dilatation of all cardiac cavities, akinesia of the anterior wall of the left ventricle (LV) and interventricular septum (IVS), impaired diastolic function of the myocardium, reduced myocardial contractility: ejection fraction (EF) 37 %, a loose blood clot in the LV apex (1.9×1.2 cm), unchanged aorta and valves. These changes were interpreted as signs of dilated cardiomyopathy (DCMP). The patient was discharged with the final diagnosis: moderate novel coronavirus infection, caused by COVID-19; DCMP, sinus tachycardia; class 3 cardiac insufficiency with low LV EF (37 %), functional class (FC) 3. LV blood clot, for additional consultations at the Academician Shumakov National Medical Research Centre of Transplantology, Moscow. According to the patient, within 2–3 days after discharge, his condition deteriorated rapidly: fever up to 38 °C, worsening of shortness of breath and oedema, fatigue; all this was a reason for urgent hospitalisation to the Cardiac Unit of the State Budgetary Healthcare Institution of the Republic of Crimea N. A. Semashko Republican Clinical Hospital, Simpheropol.

Condition upon admission: moderately severe, the patient is lucid, sensible; without hyperthermia; auscultatory, respiratory breathing is harsh, weakened in inferolateral sections; without wheezing; respiratory rate (RR): 16/minute; SpO2 99 % without additional O2; muffled, rhythmic heart tones; heart rate (HR) = pulse = 94 bpm; blood pressure (BP): 85/55 mm Hg (with bisoprolol); rhythmic pulse with satisfactory volume; oedematic shins. Clinical blood assay and blood biochemistry show signs of active inflammation: high WBC levels ($15.8*10^9$/L) with left shift (banded neutrophils: 16 %), high erythrocyte sedimentation rate (ESR) (30 mm/h), C-reactive protein (CRP) (102.3 mg/L), ferritin (451 μg/L). All other blood biochemistry parameters are unremarkable. *ECG:* sinus rhythm; HR: 81 bpm, cardiac electrical axis (CEA) is misaligned to the left, left anterior fascicular block, impaired repolarisation processes of the anteriolateral myocardial wall.

With the standard therapy in accordance with the clinical guidelines, the patient's condition was stable, moderately severe, for a week. However, on day 8 of hospitalisation, his condition deteriorated: marked shortness of breath, moderate low-productive cough and hyperthermia developed. Upon examination: severe general condition, lucid, deferred; body temperature: 37.8 °C; auscultatory, breathing is harsh, weakened in lower basal and middle sections, with areas of dry and small bubbling rale, crepitation is more marked to the right; respiratory rate (RR): 22, SpO2: 96.9 % (without additional O2); muffled, rhythmic heart tones; HR: 86 bpm; BP: 90/70 mm Hg; soft, painless abdomen; liver +2 cm; oedematic shins and feet.

During hospitalisation, the following laboratory tests were performed: serum NT-proBNP (N-terminal prohormone of brain natriuretic peptide): 2,652 pg/mL; D-dimer: 2,927 ng/mL; express COVID-19 test: negative; sterile blood culture; markers of viral hepatitis, anti-HIV antibodies (AB) and Wassermann reaction (WR): negative; thyroid hormones: normal; blood test for anti-SARS Cov-2 antibodies (ELISA): IgA — 2.4; IgM — 6.5; IgG — 12.2.

Imaging examinations: chest computed tomography (*chest CT)* revealed bilateral multisegmental viral pneumonia; 24-hour Holter monitoring recorded polyfocal ventricular extrasystoles (approx. 350 within one day), including paired; 3 paroxysmal unstable ventricular tachycardia (3–5 consecutive complexes); rare polyfocal supraventricular extrasystoles (approx. 300 within one day), including paired and group; 4 paroxysmal unstable supraventricular tachycardia; ST and T: unremarkable; QT: normal. Transthoracic *ecoCG (Figure 1)* revealed marked dilatation of all cardiac cavities: left atrium (LA) — 5.6 cm, LA volume index — 92 mL/m^2, left ventricle end-diastolic dimension (LVEDD) — 7.3 cm, left ventricle end-systolic dimension (LVESD) — 6.4 cm, left ventricular end-diastolic

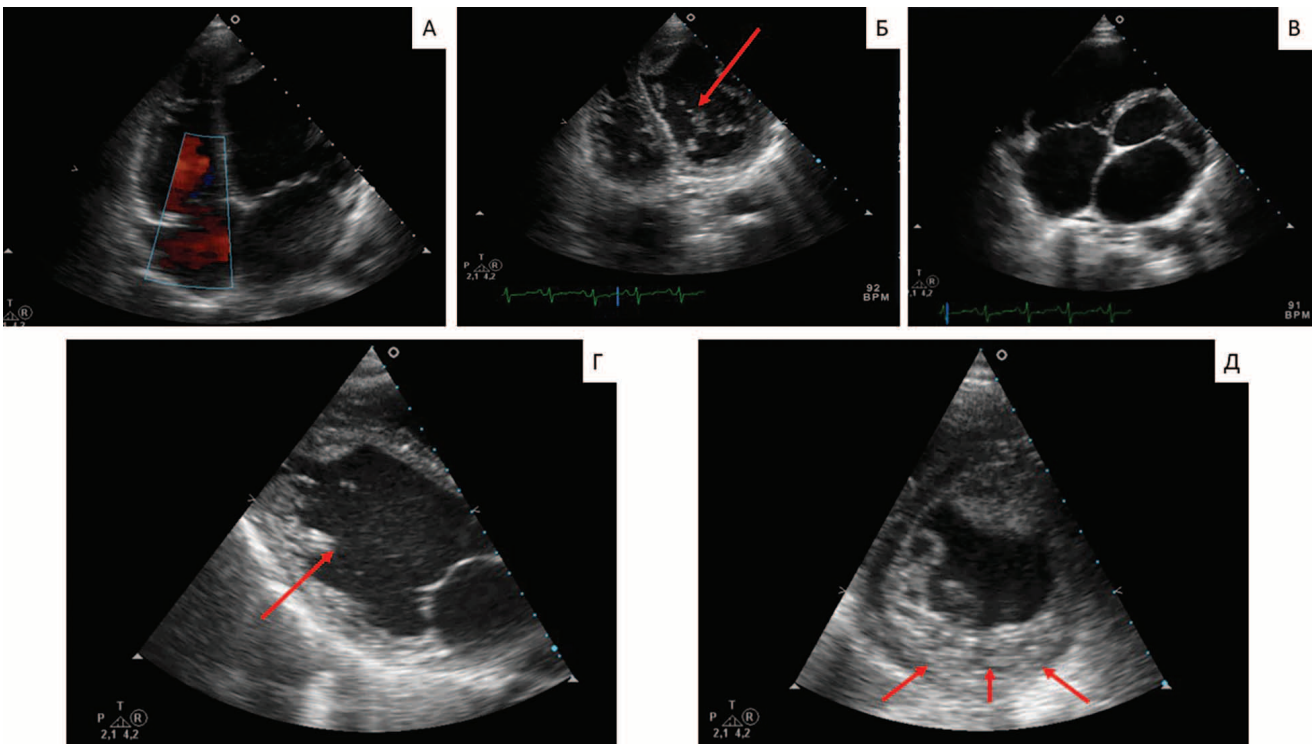
volume (LVEDV) index: 140 mL/m^2, left ventricular posterior wall thickness (LVPWT) — 1.0 cm, interventricular septum thickness (IVST) — 0.9 cm, Simpson LVEF — 18 %, right ventricle (RV) — 3.5 cm, right atrum (RA) — 6.1×7.7 cm; LV myocardium with signs of non-compaction; close to the LV apex there is a moderately echo-dense, echo-nonhomogeneous, irregular fixed blood clot (4.2×2.8×1.9 cm); at the bottom of the interventricular septum (IVS) there is a fixed, hardly moving, moderately echo-dense, echo-nonhomogeneous, irregular blood clot (2.4×1.8×1.2 cm); spontaneous blood contrasting in all cardiac cavities and inferior vena cava, moderate relative mitral and tricuspid insufficiency (TAPSE = 0.9 cm); signs of moderate pulmonary hypertension, with systolic pulmonary pressure of up to 44 mm Hg; myocardial contractility of left and right ventricles is extremely, almost diffusely reduced; 150 mL of free fluid in the pericardial cavity. *Lower limb ultrasound examination* revealed phlebothrombosis of the anterior tibial vein (ATV) of both feet.

Other organs and test results are unremarkable.

Based on the *clinical diagnosis*: primary disease — severe acute diffuse infectious myocarditis, blood clot in LV cavity; comorbidity: primary cardiomyopathy, noncompact LV myocardium; concurrent diseases: severe community-acquired bilateral multisegmental pneumonia, unspecified; complications: stage 3 cardiac insufficiency with reduced ejection fraction (EF 18 %); standard doses of pathogenetic and symptomatic medications, including diuretics (furosemide, spironolactone), deintoxication agents, antibacterial drugs (levofloxacin, ceftriaxone), anti-inflammatory therapy (dexamethasone) and anticoagulants (fraxiparine).

Despite the therapy, on day 25 of hospitalisation the patient developed acute cerebrovascular event (ACVE): aphasia, right-sided hemiparesis, and was urgently transferred to the Regional Vascular Center (RVC). During examination on January 28, 2022, the patient did not raise any complaints due to the severity of his condition, and did not answer any questions. The most probable cause of the cerebrovascular event is a combined multisystemic pathology (acute myocarditis, stage 3 cardiac insufficiency, EF 18 %, LV blood clot, bilateral multisegmental pneumonia). The intensive care was hardly efficient. During the following three days after transfer to the RVC, symptoms were aggravating; on day 3, the patient died.

Changes in parameters of the clinical blood assay during hospitalisation show reduction of the systemic inflammatory reaction (WBC count lowering, normalised ESR) up to the last day before transfer to the RVS (January 28, 2022), when there was a sharp increase in WBC count to 14.6*10^9/L with the right shift (band neutrophils — 11 %).



Picture 1. *Transthoracic echocardiography findings. А — dilation of all chambers of the heart, apical position along the long axis; Б — thrombus in the heart cavity, apical position along the long axis; В — dilation of all chambers of the heart, apical position along the short axis; Г — thrombus in the heart cavity, parasternal position along the long axis; Д — trabecular structure of the myocardium, parasternal position along the short axis.*

Table 1. *D-dimer, white blood cells, band neutrophils dynamics during hospital stay.*

Date	14.12	23.12	13.01.22	19.01.23	24.01.23	28.01.23
D-dimer (ng/ml)	2927	1245	5256	8609	7034	5196
Band neutrophils (%)	13	13	11	11	9	11
White blood cells (*10^9/L)	15,8	14,1	12,7	12,3	9,6	14,6

Over the entire period of hospitalisation, the patient's D-dimer levels (Table 1) were high, which had a direct impact on the risk of thrombotic complications and death. COVID-19 significantly increases these risks due to macro- and microvascular disorders, which are common among these patients [9]. This patient was not an exception; he had LV blood clot in a week after hospitalisation to the COVID centre.

Autopsy results

Heart: 560 g, 14×13×10 cm, rounded apex, formed by RV and LV; dilated cardiac cavities; perimeter of right atrioventricular foramen (AVF) — 13 cm, left — 12 cm. Parietal endocardium near anterior wall of LV transiting to the apex and IVS, pale, whitish, with brown fixed thrombotic masses of 1.7×0.6 cm, 0.7×0.4 cm (corresponds to fragmented blood clots in LV cavity seen of echoCG), multiple crumb-like thrombotic overlaps. Pattern of papillary muscles and trabeculae is accentuated; left ventricle wall thickness (LVWT) — 2.3 cm, right ventricle (RV) — 0.5 cm, IVS — 2.0 cm. Cusps: unremarkable. Myocardium is elastic, red-brownish, with areas of uneven repletion. Coronary artery foramens are not narrowed.

Histology. Heart: endocardium is thickened, oedematic, with loose lymphohistiocytic and leukocytic infiltration, overlaps of erythrocytic fibrinous thrombotic masses; thrombotic masses with areas of repatency, organisation and leukocytic infiltration. Uneven cardiac myocyte hypertrophy with focal interstitial fibrosis. Pronounced diffusive focal leukocytic infiltration of interstitial tissue, interstitial oedema, focal haemorrhaging. Papillary muscles fibrosis. Perivascular and intermuscular areas of loose fibrotic tissue. Foramens of some vessels have erythrocytic fibrinous blood clots, leukocyte aggregations.

Brain: area of softening, where histological pattern is blurry; peripheral focal haemorrhaging, marked glial oedema and rarefication. Foramens of some vessels have erythrocytic fibrinous blood clots, leukocyte aggregations. Uneven vascular congestion.

According to autopsy results, the death was caused by progressive brain swelling with brain stem dislocation.

Discussion

The COVID-19 pandemic attracted attention to the definite relationship between coronavirus infections and cardiovascular diseases. The growing volume of data suggests that cardiovascular involvement in COVID-19 is diagnosed mostly in middle-aged male patients; disease is severe and is associated with poor prognosis and high mortality rates [10]. Also, there are reports on late cardiovascular complications after the treatment of acute symptoms of the novel coronavirus infection. These facts were observed in this clinical case, where the patient developed inflammatory cardiomyopathy, which progressed and resulted in the patient's death 1.5 month after COVID-19 diagnosis.

In this patient, decompensated CI with reduced ejection fraction was a primary condition both at admission and during hospitalisation. Taking into account the young age, no prior cardiac diseases and arterial hypertension, ischaemic heart disease, atrial fibrillation, cardiac defects and diabetes mellitus, the relevant primary underlying diseases of CI were ruled out. Differential diagnosis of the causes of myocardial dysfunction was limited to DCMP and acute myocarditis. Since the patient had a history of the novel coronavirus infection as the most probable cause of the disease, diagnostic search was limited to acute infectious myocarditis.

Upon admission, the patient presented with weakness and reduced tolerance to physical exercise, corresponding to the results of recent meta-analyses, which revealed prevalence of non-specific clinical symptoms in patients with COVID-19-associated myocarditis, such as shortness of breath, fever and cough [11]. Similar complaints are presented by COVID-19 patients who do not have associated cardiovascular inflammatory disorders and are signs of respiratory involvement. More specific symptoms, such as cardiac irregularities, false angina, were not significant, which makes diagnosis of cardiovascular complications much more challenging. During hospitalisation, patients have high pro-inflammatory markers (high WBC count with the right shift, high ESR, at least 5-fold increase in CRP, 1.5-fold increase in ferritin levels), which can be interpreted as hyperinflammatory COVID-19 stage. This hypothesis is confirmed by the steady growth of CRP (27–84 mg/L) and D-dimer (1,245–8,609 ng/mL) levels despite steroid anti-inflammatory therapy.

In this case study, signs of myocardial damage were changes seen on ECG: blocked anterior left His band branch, paroxysmal, polyfocal arrhythmias; cardiomegaly as seen on chest X-ray; echoCG showed significant dilatation of all cardiac cavities, signs of biventricular insufficiency, as well as EF 18 % and pericardial effusion. ECG pattern suggests myocardial dysfunction. Myocardial damage and biventricular dilatation caused significant increase in NT-proBNP levels to 2,652 pg/mL. A study by Chinese researchers showed direct correlations between NT-proBNP levels and death, and this correlation persisted after a multifactor analysis with due account of all known predictors of death [12]. The starting point for this biomarker was 88.64 pg/mL; any higher levels were associated with a higher risk of death at the hospital, where NT-proBNP sensitivity and specificity were 100 % and 66.7 %, respectively.Therefore, initial prognosis for this patient was very poor, with NT-proBNP levels 30 times exceeding the starting point value.

Multiple blood clots in lower limbs and LV of this patient, which kept growing despite anticoagulants, confirm suggested excessive activation of coagulative blood stasis caused by a significant increase in pro-coagulation agents [13].

Taking into account echoCG signs of myocardium non-compaction and autopsy results (uneven cardiac myocyte hypertrophy with focal interstitial fibrosis), noncompact cardiomyopathy (NCCMP) was verified in this patient. It was impossible to have a detailed life history, including a family history, since there were no previous medical records and close relatives. NCCMP, which was diagnosed for the first time during hospitalisation, is likely to have caused aggravation of acute infectious myocarditis and impacted the prognosis. According to a meta-analysis (Aras D. et al., 2006), factors, associated with poor prognosis in patients with NCCMP without any concurrent inflammatory involvement of the myocardium, are delated LV, reduced LV EF and MRI-confirmed myocardial fibrosis [14]. It was impossible to assess dilatation or reduced systolic function of LV before hospitalisation because there were no indications of NCCMP in medical records; while during admission, both these criteria were very high.

An additional factor, which has negative effect on the prognosis, is turbulent haemodynamic intracardiac flows and their slowdown in lacunae, which contribute to clotting, similar to those observed in this case study. Prior to admission to the Cardiology Unit on December 21, 2021, echoCG showed a blood clot near LV apex (1.9×1.2 cm), which kept growing, and on January 10, 2020, it was 4.2×2.8×1.9 cm. Another 2.4×1.8×1.2 cm blood clot formed in the bottom part of IVS, despite anticoagulation therapy. This observation corresponds to literature sources, according to which clinical presentation of NCCMP is prevailed by the following triad: CI, arrhythmia (ventricular tachycardia and atrial fibrillation) and systemic thromboembolism [15]. We think that the cause of the cardioembolic fatal ACVE was fragmentation of LV blood clots, the fragments of which were found in autopsy both in LV cavity and brain vessel foramina.

Limitations of this clinical case

We were unable to perform some modern imaging examinations, such as PET or CVMR and endomyocardial biopsy due to technical reasons; therefore, intravital histological verification of myocarditis and virus genome identification were not conducted, which is a significant diagnostic drawback. However, this drawback is rather a regularity than an exception. Literature sources show that very often COVID centres are only able to verify myocarditis with standard examination techniques: ECG and echo CG, as well as biomarkers (troponins, brain natriuretic peptide, CRP, D-dimer, etc.) [16, 17].

Conclusions

This case study emphasises the significance of clinical, laboratory and imaging monitoring of cardiovascular functions and inflammatory biomarkers in patients who recently had the novel coronavirus infection or have a long-lasting disease, in order to ensure early diagnosis of myocardial damage, rapid correction of this complication and prevention of any negative outcomes of COVID-19.

Further studies of pathogenic mechanisms behind myocardial dysfunction in COVID-19 are essential for risk classification and development of diagnostic criteria for myocarditis, as well as development of efficient methods for prevention and treatment of this complication. The possibility of objective assessment of the short-term and long-term prognosis in this population is one of the priority areas in reduction of cardiovascular mortality.

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