### **Case Report**

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# Development of Rhabdomyolysis in the Long-term Period of Previous New Coronavirus Infection COVID-19 (Clinical Case Report)

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RELEVANCE Rhabdomyolysis is one of the complications of the new coronavirus infection COVID-19, which may cause acute kidney injury (AKI). The reason for the development of rhabdomyolysis in our observation in a patient after suffering COVID-19 in the long-term period was an increased muscle load.

AIM OF STUDY Presentation of a case of rhabdomyolysis with AKI in a patient after COVID-19 in the long-term period.

MATERIAL AND METHODS In clinical observation, a 25-year-old patient L. is presented, who was being treated in the Department for the Treatment of Acute Endotoxicosis of the N.V. Sklifosovsky Research Institute for Emergency Medicine. In 2020, he developed COVID-19, complicated by rhabdomyolysis and AKI in the long term period.

RESULTS Examination revealed an increase in creatinine phosphokinase (CPK) - 106,000.0 U/L, alanine aminotransferase (ALT) - 553.0 U/L, aspartate aminotransferase (AST) - 1582.0 U/L, lactate dehydrogenase (LDH) - 2809.0 U/L, levels of serum creatinine 164  $\mu$ mol/L and myoglobin - 201 ng/ml. Virological research: IgM - 0.27 units per ml; IgG - 7.28 units per ml. 3 Three-phase scintigraphy with 99mTc-pyrfotech revealed signs of necrotic changes in the muscles of the upper half of the back, muscles of the chest (mainly on the right), muscles of the shoulder and upper half of the forearm on both sides. Kidneys: decreased perfusion of the right kidney (relative to the left), moderate slowdown of urodynamics at the level of the calyx-pelvis complex on both sides.

CONCLUSIONS The reason for the development of rhabdomyolysis in the long-term period in the patient after suffering from COVID-19 was an increased muscle load. Targeted research and medical history can help identify signs of rhabdomyolysis. The use of the radionuclide diagnostic method makes it possible to identify areas of soft tissue damage with a one-step assessment of renal function in rhabdomyolysis in the acute period of the disease, as well as to evaluate the effectiveness of treatment with dynamic observation. When rhabdomyolysis is confirmed, it is necessary to carry out detoxification and infusion therapy, to monitor renal function in order to detect acute kidney injury, and in case of deterioration of renal function and intoxication, renal replacement therapy is indicated.

Keywords: new coronavirus infection COVID-19, coronavirus SARS-CoV-2, acute kidney injury, scintigraphy, rhabdomyolysis

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AKI — acute kidney injury

ALP — alkaline phosphatase

AST — aspartate aminotransferase

COVID-19 — new coronavirus infection COVID-19

CPK — creatine phosphokinase

HR — heart rate

LDH — lactate dehydrogenase

#### **INTRODUCTION**

The SARS-CoV-2 coronavirus was identified at the end of 2019 in the Chinese province of Wuhan, and in 2020, an increase in the number of cases led to a pandemic that covered most countries of the world. The main manifestations of coronavirus are considered to be the damage to the upper respiratory tract and lungs with the development of bilateral pneumonia of varying severity, acute respiratory distress syndrome, and acute renal failure. Patients of all ages are susceptible to the infection, and the most severe course is observed in patients with concomitant diseases, including various diseases of the cardiovascular system, lungs, liver and kidneys [1].

Rhabdomyolysis is one of the factors contributing to the development of acute kidney injury (AKI) in a patient after a new coronavirus infection COVID-19. In the foreign literature, there are reports of adult patients infected with the SARS-CoV-2 coronavirus, who either experienced muscle pain at the beginning of the disease, or developed muscle damage in the form of rhabdomyolysis as a late complication during hospitalization. Signs of rhabdomyolysis in some cases were accompanied by an increase in blood levels of creatine phosphokinase (CPK) up to 43,000 U/L, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and lactate dehydrogenase (LDH). In severe cases, rhabdomyolysis led to AKI and was considered a characteristic manifestation of COVID-19 or its later complication [2-6].

**The aim of the study** was to describe a case of AKI developed in a patient in the long term period after he has had COVID-19)

#### MATERIAL AND METHODS

The clinical case includes a 25-year-old patient L., who was treated in the Acute Endotoxicosis Treatment Department of N.V.Sklifosovsky Research Institute for Emergency Medicine. In 2020, he was ill with COVID-19, which was complicated by the development of rhabdomyolysis and AKI.

He became ill on April 13, 2020, when he noticed an increase in body temperature to 37.4-37.9°C and had dry cough. A polymerase chain reaction (PCR) test of April 13 was positive, the blood level of antibodies was normal. Computed tomography of April 13 revealed a single area of consolidation with ground-glass opacity in the lower lobe of the left lung (CT-1). The patient was diagnosed with "New coronavirus infection COVID-19". He was treated at home. On an outpatient basis, the treatment performed included antibacterial therapy: levofloxacin 500 mg once a day for 4 days, then azithromycin 500 mg once a day for 2 weeks. After 2 weeks, he noted a repeated increase in body temperature to 39.0-40.0°C, weakness, headache, loss of taste, lethargy, asthenia. The patient was prescribed the treatment with azithromycin (repeated course) 500 mg once a day for 2 weeks and hydroxychloroquine 200 mg twice a day for 9 days. The PCR test of May 25 was negative, IgM antibodies to SARS-CoV-2 made 0.22 IU/mL, IgG antibodies to SARS-CoV-2 made 1.07 IU/mL. The patient was treated at home. The treatment had a positive effect. In the next 2 months, weakness and taste disorders persisted.

On September 4, 2020, the patient came to the Emergency Department of N.V.Sklifosovsky Research Institute for Emergency Medicine with complaints of weakness, muscle pain in the upper extremities and back, and aching pain in the lower back, and a changed color of urine (dark urine) that have emerged over the week prior to his visit to the Institute after visiting the fitness centre where he performed strength exercises for different muscle groups. It should be noted that before the coronavirus infection, the patient constantly visited the gym and performed these exercises without any negative consequences.

Upon admission, the respiratory rate (RR) was 18/min; heart rate (HR) was 90 beats/min; body temperature was 36.6°C, blood oxygen saturation (O2 saturation) 98%. On physical examination: the lung auscultation showed moderate weakened respiration, no wheezing, clear heart sounds, blood pressure (BP) was 120/70 mm Hg, HR was 78 beats/min, the abdomen was soft and painless at palpation. Blood tests of September 3, showed an abrupt increase in blood levels of CPK to 106,000.0 U/L, ALT 371.6 U/L (maximum value of 553.0 U/L on September 4), AST 1504.9 U/L (maximum value of 1582.0 U/L on September 4) and LDH 2809.0 U/L. The baseline level of serum creatinine was 91.6 mmol/L (on September 7, an increase to 164 mmol/L was noted) (Table 1). In the blood biochemistry test of September 7, an increased level of myoglobin up to 201 ng/mL was also noted. The urinalysis of September 4 showed protein 0.7 g/L, red blood cells 0-2 per field of vision, white blood cells 3-8 in the field of vision, single granular casts (Table 2). No changes were detected in the complete blood count and coagulogram. The PCR test of September 3 was negative. The test for anti-SARS-CoV-2 antibodies of September 3 showed IgM 0.27 IU/mL; IgG 7.28 IU/mL. Virological assay of September 8 for antibodies against the Australia hepatitis B virus surface antigen (HBs-Ag), viral hepatitis C (HCV) and human immunodeficiency virus (HIV) were negative, Wasserman reaction was negative.

Table 1
The results of biochemical blood test dynamics of patient L.

Laboratory parameter, units	Date of sampling, result						Reference values
	03.09	04.09	05.09	07.09	08.09	14.11	7
Creatinine, µMol/L	91.6	79.2	88.5	164		89.1	74.0-110.0
Urea, mmol/L	5.3	3.8	3.8	19.8		4.9	1.8-7.2
Alpha-amylase, U/L	44.1				41.1	46.7	28.0-100.0
ALT, U/L	371.6	553.0	323.0		179.3	37.5	0.0-45.0
AST, U/L	1504.9	1582.0	559.0		150.1	25.0	0.0-35.0

CPK, U/L	106000.0	53760.0	10859.0		1635.0	82.6	0.0-171.0
GGTP, U/L					14.91		0.0-45.0
AP, U/L	67.2	23	19		60.2	178.5	30.0-120.0
LDH, U/L	2809.0	1090.0	203.0		97.0	274.3	0.0-248.0
Total protein, g/L	66.2		65.0		61.2	67	66.0-83.0
Total bilirubin, µMol/L	13.5				10.9	16.6	5.0-21.0
Iron, µMol/L	12.3				23.2		12.5-32.2
Myoglobin ng/mL				201			70.0-100.0
Glucose, mmol/L					4.3	4.8	
Total potassium, mMol/L	4.56			4.09	4.45	3.2	3.5-5.1
Sodium, mMol/L	140.4				141.6	139	135.0-145.0
Chlorine, mMol/L	105.3				103	101	98.0-106.0
Cholesterol, mMol/L	5.3				4.5		3.2-5.2
Cholinesterase, kU/L	7.8						4.62-11.5
Bile acids, mmol/L	7.2				8.6		0.0-8.1

Notes: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; GGTP, gamma-glutamyl transpeptidase; AP, alkaline phosphatase; LDH, lactate dehydrogenase.

Table 2 The results of urinalysis dynamics of patient L.

Laboratory parameter,		Reference values		
units	04.09	07.09	14.11	
Relative density	1.028	1.028	1.025	1.008-1.025
pH, U	6.0	5.5	6.0	5.5-7.0
Protein in urine, g/L	0.7	0.2	0	0.0-0.1
Glucose, semi-quantitative mmol/L	0	0	0	0.0-0.08
Bilirubin, µmol/L	0	0	0	0
Ketones, µmol/L	0	0	0	0
Squamous epithelial cells, in f./v.	Single cells in the preparation	Insignificant amount	No	0
Leukocytes, in f./v.	3-5-8	1-3	2-3	0-5.0
Abnormal erythrocytes, in f./v.	0-1-2	0-1	1-3	0
Granular casts	Single cells in the preparation	0	0	0
Hyaline casts	0-1.0	0	0	0-1.0
Mucus in urine	Insignificant amount	Moderate amount	0	Insignificant amount

Instrumental investigations. The electrocardiogram (ECG) of September 3 showed sinus rhythm, arrhythmia, heart rate 71-94 beats per min, PQ interval 0.12. The conclusion was "Sinus arrhythmia, without pathology". According to the results of an ultrasound examination of the abdominal organs and kidneys of September 5, the signs of diffuse changes in both kidneys were found.

High levels of AST, LDH, and CPK enzymes, abnormalities in urinalysis results, and the signs of bilateral diffuse changes in the renal parenchyma (according to the renal ultrasonography) made it possible to suspect the presence of rhabdomyolysis complicated by AKI.

Since the examination algorithm for patients with positional soft tissue compartment syndrome and rhabdomyolysis in N. V. Sklifosovsky Research Institute for Emergency Medicine includes a radionuclide method (a three-phase scintigraphy with 99mTc-pirfotech) [23-25], which allows a kidney function assessment and the identification of muscle necrosis areas (Patent for Invention No. 2207880, 2003) at a single intravenous administration of a radiopharmaceutical, the patient underwent a radionuclide study on September 7. The three-phase scintigraphy with 99mTc- pirfotech revealed the signs of necrotic changes of the upper back muscles, chest muscles (mostly right), muscles of the shoulder and upper half of the forearm on both sides (Fig. 1). As for the kidneys, a decreased perfusion of the right kidney (compared to the left one), a moderate slowdown of urodynamics at the level of the calyx-pelvic complex on both sides (Fig. 2)



Fig. 1. Scintigrams of 25-year-old male patient L., dated 7 Sept, 2020 in the whole body mode in the anterior and posterior projections in the tissue and bone phases: foci of muscle necrosis (with an increase in the relative accumulation of the radiopharmaceutical in the bone phase) in the projection of the muscles of the upper back, chest muscles (mainly on the right), shoulder muscles and upper forearm (indicated by arrows) are visualized

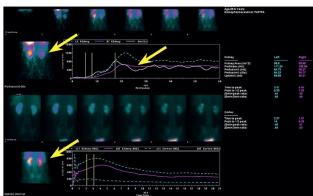


Fig. 2. Scintigrams of the kidneys of 25-year-old male patient L., dated Sept 7, 2020; in dynamic mode: renograms of the parenchymal type with a decrease in perfusion on the right (visual decrease in the accumulation of the radiopharmaceutical and a decrease in the amplitude of the renogram) and a moderate uptake of the radiopharmaceutical in the calyx-pelvic complex of both kidneys (indicated by arrows)

The PCR test of September 15 was negative, IgM antibodies against Coronavirus (SARS-CoV-2) made 0.28 IU/mL, IgG antibodies against Coronavirus (SARS-CoV-2) made 5.99 IU/mL.

Based on clinical, laboratory, ultrasound and three-phase scintigraphy data with 99mTs-pirfotech the following diagnosis was made: "AKI associated with non-traumatic rhabdomyolysis (affected muscles of the back, chest, shoulder and forearm on both sides). Toxic hepatitis".

In hospital, the patient underwent detoxification and fluid therapy (0.9% sodium chloride 400 ml, 10% glucose 400 ml, isotonic sterofundin 500 ml), omeprazole 40 mg/day, amlodipine 10 mg/day, ursofalk 1000 mg/day. For the purpose of detoxification, 2 plasmapheresis procedures were performed on day 1 (September 4) and day 4 (September 7) of the patient's hospital stay. The volume of removed plasma was a total of 4000 ml.

During treatment, the patient's condition improved, and the AKI signs regressed. Blood tests before discharge from hospital (on September 8) showed signs of toxic hepatitis (moderate increase in blood AST, ALT, and CPK values, see Table 1). The patient was discharged from hospital in a satisfactory condition to be followed-up by a nephrologist, general practitioner, and gastroenterologist in the outpatient clinic at the place of residence.

On November 12, 2020, the patient underwent repeated three-phase scintigraphy with 99mTc-pirfotech as an outpatient, which showed a marked positive dynamics in the patient: there were no muscle necrosis foci compared to the study of 07.09.20 (Fig. 3). A control biochemistry blood test of November 14 showed all biochemical parameters returned to normal (except for alkaline phosphatase making 178 U/L) (Table 1).

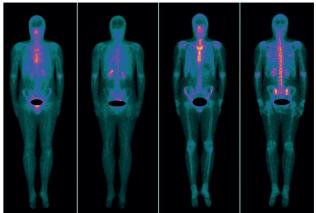


Fig. 3. Scintigrams of 25-year-old male patient L., dated Nov 12, 2020 in the whole body mode in the anterior and posterior projections in the tissue and bone phases: the absence of foci of muscle necrosis (compared to the study dated Sept 7, 2020)

#### **DISCUSSION**

Rhabdomyolysis may develop as a result of sustained injuries, infection, excessive physical exertion, myopathy, and metabolic syndrome, as well as in other conditions that may lead to muscle tissue destruction and the entry of the decay products into the systemic circulation, as evidenced by the elevated blood levels of CPK, transaminases, LDH, aldolase, myoglobin, potassium, phosphates, nitrogenous bases [7]. In most cases, the cause of rhabdomyolysis is considered to be a comatose state due to alcohol intoxication or narcotic drug overdoses [8-11]. The incidence of rhabdomyolysis ranges from 5% to 11%, with a significant number of cases remaining undiagnosed [7, 12]. A high concentration of myoglobin has a direct nephrotoxic effect, which can lead to the obstruction of the renal tubules and cause the AKI development [13, 14].

The literature has described myositis cases when infected with influenza viruses "A" and "B", enterovirus, human immunodeficiency virus, cytomegalovirus, Epstein–Barr virus, and herpes simplex virus [15-17]. According to Wu V. et al., the severe acute respiratory syndrome (SARS) (not COVID-induced SARS) was associated with rhabdomyolysis [18, 19].

The mechanism of rhabdomyolysis development in COVID-19 is not fully understood. Most likely, according to the proposed general principles and mechanisms described under the action of other viruses, the following occurs: 1) a direct viral invasion leading to a muscle destruction; 2) a sustained immune response to the virus, which causes a "cytokine storm", leads to damage to muscle tissues and direct destruction of muscle cells by circulating viral toxins [7, 17, 20, 22]. Based on the presence of elevated inflammatory markers found in the muscle biopsies of patients infected with the SARS-CoV-2 coronavirus, Chen L. et al., suggested that rhabdomyolysis in those patients was caused by a "cytokine storm" [20].

Wen Z. et al. suggested that the use of hydroxychloroquine might also contribute to the late development of rhabdomyolysis in patients suffering from COVID-19 [21].

In our clinical case, rhabdomyolysis developed in a patient who had had a coronavirus infection 3-4 months after the onset of the disease. The relation to the viral infection is obvious, since the muscle damage occurred despite many years of habitual physical activity for the patient, which previously did not cause any consequences. The cases of rhabdomyolysis presented in the literature are relevant in the acute period of the disease and during hospitalization. Three foreign publications describe cases of rhabdomyolysis as a possible late complication associated with COVID-19 [6, 26, 27].

#### CONCLUSION

The obtained results have confirmed that it is necessary to take into account muscular loads as a factor in the development of rhabdomyolysis in the long-term period in a patient after suffering COVID-19. The possible effect of hydroxychloroquine in the therapeutic dosage on the development of muscle damage requires further studying and statistical justification.

#### **FINDING**

- 1. Conducting targeted investigations and collecting medical history help to identify signs of rhabdomyolysis.
- 2. An increased muscular load has been the cause of the rhabdomyolysis development in the long-term period in a patient after suffering COVID-19.
- 3. If patients with COVID-19 develop myalgia, asthenia, or muscle pain in the early and long-term periods, they should be examined to exclude rhabdomyolysis by performing a biochemistry blood test to determine the levels of creatine phosphokinase, myoglobin, lactate dehydrogenase, and aspartate aminotransferase.
- 4. Using the radionuclide diagnostic method allows us to identify the affected soft tissue areas and simultaneously assess the renal function in rhabdomyolysis in the acute period of the disease, as well as to evaluate the treatment efficacy by dynamic observation.
- 5. If rhabdomyolysis has been confirmed, it is necessary to conduct detoxification and fluid therapy, monitor the kidney function in order to detect acute renal injury, and in case of a deteriorated renal function and intoxication, a renal replacement therapy is indicated.

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