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I.L. Vysochyna¹,
T.P. Nikolaenko-Kamyshova¹,
O.M. Biesiedin²

**POSTCOVID SYNDROME: REGARDING
 THE RISKS OF DEVELOPING THROMBOTIC
 COMPLICATIONS IN PATIENTS WITH
 ISCHEMIC LIMB LESIONS
 (clinical cases)**

*Dnipro State Medical University*¹

V. Vernadsky str., 9, Dnipro, 49044, Ukraine

e-mail: vysochynail@gmail.com

*Municipal non-profit enterprise «City Clinical Hospital No. 4» of Dniprovsk City Council*²

Blyzhnia str., 31, Dnipro, 49000, Ukraine

e-mail: bam-86@ukr.net

*Дніпровський державний медичний університет*¹

вул. В. Вернадського, 9, Дніпро, 49044, Україна

*КНП «Міська клінічна лікарня № 4» Дніпровської міської ради*²

вул. Ближня, 31, Дніпро, 49000, Україна

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Abstract. Postcovid syndrome: regarding the risks of developing thrombotic complications in patients with ischemic limb lesions (clinical cases). Vysochyna I.L., Nikolaenko-Kamyshova T.P., Biesiedin O.M. *The problem of postcovid syndrome is currently relevant, since in the stabilization of vital functions, the processes of immunological inflammation with significant disorders of endothelium functions continue; this causes tissue ischemization, especially in the presence of changes at the level of microcirculation in patients with angiopathy and vasculopathy. It is noted that in COVID-19 comorbidity with hypertension, coronary heart disease, diabetes mellitus, systemic connective tissue diseases the risks, course, prognosis and development of vascular complications significantly increase. The severity of the inflammatory process and predicting the likelihood of complications is accompanied by changes in laboratory indicators, namely: in the general blood test – leukocytosis, an increase in the level of neutrophilic granulocytes, a decrease in the content of hemoglobin and platelets; in biochemical indicators – a decrease in the level of the general protein, an increase in the indicators of alanintransferase, aspartaminotransferase, C-reactive protein, lactat-dehydrogenase, ferritin; coagulation changes – increase in the level of fibrinogen, D-dimer, reduction of activated partial thromboplastin time. On the basis of the considered clinical cases, taking into account modern ideas about the peculiarities of the development of thrombotic complications in COVID-19 infection in patients with ischemic lesions of the extremities, the need to prescribe low molecular weight heparin as a selection drug for the treatment of thrombophilic conditions has been proven. Detailed study of histological material is important for establishing changes at the level of microcirculation and ischemization of tissues, this will allow to develop algorithms for the treatment and prevention of complications. Solving these issues, not only in the presence of COVID-19, but also in any stressful cases, requires careful clarification of the mechanisms for the development of complications and a timely adequate integrated approach to treatment to improve and stabilize the condition of patients.*

Реферат. Постковидный синдром: относительно рисков развития тромботических осложнений у пациентов с ишемическими поражениями конечностей (клинические случаи). Высочина И.Л., Николаенко-Камышова Т.П., Беседин А.М. *Проблема постковидного синдрома в настоящее время актуальна, поскольку при стабилизации витальных функций продолжается процесс иммунологического воспаления с нарушениями функций эндотелия, вследствие чего у больных с ангиопатиями и васкулопатиями нарастают проявления ишемизации тканей. Отмечено, что при коморбидности COVID-19 с гипертонической болезнью, ишемической болезнью сердца, сахарным диабетом, системными заболеваниями соединительной ткани значительно повышаются риски неблагоприятного течения, прогноза и развития сосудистых осложнений. Степень тяжести воспалительного процесса и прогнозирование вероятности развития осложнений подтверждаются изменениями лабораторных показателей, а именно: в общем анализе крови – лейкоцитоз, повышение уровня*

нейтрофильных гранулоцитов, снижение содержания гемоглобина и тромбоцитов; в биохимических показателях – снижение уровня общего белка, повышение показателей аланинтрансаминазы, аспаратамино-трансаминазы, лактатдегидрогеназы, С-реактивного протеина, ферритина; коагуляционные изменения – повышения уровня фибриногена, Д-димера, укорочение активированного частичного тромбопластинового времени. На основании рассмотренных клинических случаев, с учетом современных представлений об особенностях развития тромботических осложнений при COVID-19 инфекции у больных с ишемическим поражением конечностей, доказана необходимость назначения низкомолекулярных гепаринов в качестве препаратов выбора для лечения тромбофилических состояний у пациентов с коморбидной патологией. Детальное изучение гистологических материалов с акцентом на изменения на уровне микроциркуляции в ишемизированных тканях позволит разработать алгоритмы лечения и профилактики осложнений. Решение этих вопросов, не только при наличии COVID-19, а и при любых стрессовых ситуациях, требует тщательного уточнения механизмов развития осложнений и своевременного адекватного комплексного подхода к лечению для улучшения и стабилизации состояния больных.

Predicting the severity, risk of complications, and length of rehabilitation period in patients after COVID-19 remains an important challenge, especially in patients with comorbid conditions. According to the experience of Chinese clinics, mortality rates of patients with COVID-19 without aggravating comorbidities were 0.9%, while in patients with diabetes – 7.3%, in rheumatic diseases – up to 10% [3, 4, 5, 7, 9, 10].

During the COVID-19 pandemic, special attention should be paid to identifying patients at increased risk for thrombosis. Unfavorable background is considered to be readiness for super-inflammatory response (congenital factors, connective tissue diseases and immunoproliferative syndromes), excessive activation of the hemostasis system in the form of hereditary, acquired thrombophilias and their combinations [1, 2, 6, 8, 12, 13].

Complications in the form of arterial and venous thrombosis in COVID-19 occur in almost 30% of cases, these are: venous thromboembolism, lesions of cerebral, coronary, renal arteries, manifestations of vasculitis and their combinations. It was found that the frequency of re-admission to the hospital in the postcovid period is 20% [2, 5].

Delaying the provision of medical care when an infectious agent is added to the course of the underlying disease with a severe vascular condition (old age, diabetes, hypertension, obesity) can lead to fatal consequences; patients with lesion of coronary arteries, heart failure and / or arrhythmias have a higher risk of death during the acute period of the disease [6, 8, 10, 12].

The severity of clinical manifestations of COVID-19 depends on several components: the sensitivity of ACE2 receptors of epitheliocytes of the mucous membranes of the respiratory tract, gastrointestinal tract, endothelial cells to the virus; its interaction with the CD147 receptor of immune cells (macrophages, monocytes, neutrophils) with subsequent production of cytokines, the formation of neutrophilic extracellular traps (Neutrophil extra-

cellular traps), the formation of leukocyte-platelet aggregates. Through electrostatic interaction, the contact internal path of blood coagulation is activated [7, 13], which deepens the manifestations of endothelial dysfunction, leads to disruption of fibrinolysis with fibrination. Completion of the pathogenetic chain is thrombosis of microvascular alveoli, kidneys and other capillaries, which is referred as "pulmonary intravascular coagulation" or "COVID-19 associated coagulopathy" (CAC) [7, 9, 11, 13].

According to the results of autopsies of patients who died from SARS-CoV-2 infection, thrombi with a large number of platelets in the microcirculatory tract of the lungs and other organs were found [13].

In a Dutch study, the incidence of venous thromboembolism (VTE) and arterial thromboembolism (ATE) among 184 patients with COVID-19 treated in intensive care units was 27% and 3.7%, respectively, according to the European Registry. (Piazza // JAMA, Nov, 23, 2020) – 35%. The most common thrombotic complication was pulmonary embolism – in hospitalized patients VTE was established in the range of 4.8%-85%. Later, the manifestations of proximal fibrotic obstruction in the large elastic pulmonary arteries and secondary microvasculopathy in the pulmonary vessels progressed [6, 14].

There is a strong correlation between markers of neutrophilic extracellular traps and the concentration of D-dimer (this mechanism is the cause of thrombosis in sepsis and oncopathology). The risk of developing arterial thrombosis is due to platelet activation (platelet adhesion, increased thromboxane A2 synthesis and Willebrand factor activity) [12]. As a result of progressive coagulopathy and disorders of microcirculation, tissue ischemia increases (at the cellular level there are manifestations of mitochondrial dysfunction and activation of the processes of anaerobic metabolism with increased lactate formation) [1].

The most sensitive laboratory markers of endothelial damage are: concentration of P selectin 20 ng/ml (N=12 ng/ml), the content of soluble CD-

4-ol receptor up to 400 pg/ml (N=120-150 pg/ml), soluble thrombomodulin – from 7 to 17 ng/ml. Determination of these markers in the initial stages of the disease would allow to establish high-risk groups for the development of vascular lesions and the feasibility of preventive measures. Unfortunately, none of these markers is tested in Ukrainian laboratories.

Severe thrombovasculitis in COVID-19 is accompanied by changes in laboratory parameters: in the full blood count there is a decrease in hemoglobin, platelets, leukocytosis with increased neutrophils and monocytes; in biochemical parameters – a decrease in total protein and albumin with increasing content of C-reactive protein, ferritin, lactate dehydrogenase, alanine transferase (ALT) and aspartate aminotransferase (AST), frequent detection of antiphospholipid antibodies; in the indicators of the coagulogram – increase in the level of fibrinogen, D-dimer, reduction of the activated partial thromboplastin time, decrease in the prothrombin index [1, 17].

At present, according to the recommendations of the International Society of Thrombosis and Hemostasis (ISTH), prophylactic doses of heparin are required for all patients hospitalized for COVID-19 infection (including critically ill patients) in the absence of contraindications. (active bleeding and platelet count less than $25 \times 10^9/L$, manifestations of renal failure) [2, 12].

After stabilization of patients, as well as for patients undergoing outpatient treatment for COVID-19, in the presence of high risk factors for thrombotic disease (over 65 years, concomitant severe chronic diseases, limited mobility, history of thrombotic episodes, malignant neoplasms, the presence of additional risk factors for thrombosis in patients not receiving anticoagulant therapy by other indicators at the level of D-dimer ≥ 500 ng/ml) it is advisable to carry out prophylactic anticoagulant therapy for up to 1 month according to the HAS-BLED scale for patients with atrial fibrillation. Increase in the prothrombin index (PTI) and activated partial thromboplastin time (APTT) are not considered contraindications to their use.

If the presence of thrombotic complications is confirmed and the possibility of their development is suspected, therapeutic doses of low-molecular-weight heparins (LMWH) should be prescribed [14, 15, 17].

The aim of the study was to analyze the manifestations of complications in patients with ischemic lesions of the limbs with past COVID-19, and an attempt to develop algorithms for diagnosis and treatment to prevent them.

The study was conducted in accordance with the principles of bioethics set out in the Helsinki Declaration on Ethical Principles for Human-Based Medical Research and the Universal Declaration on Bioethics and Human Rights (UNESCO).

An illustration of this review is the clinical cases that indicate the consequences of severe damage to the vascular system in the postcovid period.

Case history 1.

Patient Sh., 83 years old, was hospitalized on November 10, 2020 with a diagnosis of atherosclerosis of the vessels of the lower limbs. Thrombosis of the femoral-popliteal segment with ischemia of the right lower extremity 4 stage.

Secondary diagnosis: ischemic heart disease: diffuse and postinfarction (2003) cardiosclerosis (pacemaker implantation, 2005); hypertension disease stage III. (ACE, 2015). Heart failure IIB. Functional class III. Type 2 diabetes mellitus, subcompensated course. Coronavirus infection, convalescence phase. Residual manifestations of bilateral pneumonia.

The patient complained of pain, swelling of the right lower limb, discoloration of the skin – blackening, the presence of a wound in the right foot. Complaints appeared and aggravated over the past 2 weeks.

Previously, by a family doctor referral he was urgently hospitalized in the therapeutic department for COVID-19 infection, where he was from 19.10.2020 to 29.10.2020. Upon admission to the therapeutic department, the condition was assessed as severe due to increase in body temperature to 38.5 C, manifestations of shortness of breath at rest with saturation of 80%. On auscultation of the lungs – harsh breathing over all surface with moist rales in the lower departments on both sides. Heart tones are muffled, tachycardia – heart rate (HR) 108 beats per minute, blood pressure (BP) – 160/90. Analysis for COVID-19 by polymerase chain reaction (PCR) No. 046 *** dated 19.10.2020 confirmed the presence of COVID-19. According to the results of computed tomography, the presence of bilateral pneumonia of the lower part with a picture of "frosted glass" and the consolidation of foci of infiltration was established. On the electrocardiogram (ECG) from 16.10.2020 – left ventricular hypertrophy, cicatricial changes of the myocardium. Findings of routine laboratory tests without significant changes.

The patient received adequate therapy, including dexamethasone and rivaroxaban. With gradual improvement with normalization of temperature and saturation of $\geq 90\%$, the patient was transferred to outpatient treatment with recommendations for further intake of rivaroxaban 15 mg per day.

During day 3-4 of outpatient treatment, complaints related to the problem of the right lower limb, appeared and he was hospitalized in the surgical department.

Upon admission to the hospital, the general condition of the patient was assessed as moderate. Skin and mucous membranes are moderately pale. In the lungs – breathing is harsh in the lower parts it is weakened, no wheezing. Heart tones are dull, rhythmic, blood pressure – 150/90 mm Hg., heart rate – 96 beats/min. The abdomen is soft and painless. The liver and spleen are not enlarged.

Local status: the skin on the right foot is swollen, hyperemic. Pulsation in the arteries of the foot and in the femoral-popliteal segment is not determined. Ischemic tests are positive. According to vital signs, amputation of the right lower limb at the level of the middle third of the thigh is necessary.

When comparing the findings of full blood count with those in the discharge epicrisis of the therapeutic hospital, a significant decrease in hemoglobin level was noted – from 136 g/l to 92 g/l, erythrocytes – from $4.20 \cdot 10^{12}/l$ to $2.9 \cdot 10^{12}/l$ and platelets – from $213 \cdot 10^9/l$ to $78 \cdot 10^9/l$ with an increase in the level of leukocytes from $7.2 \cdot 10^9/l$ to $16.8 \cdot 10^9/l$, the presence of 17% of rod-shaped forms and 75% of neutrophils. The level of total protein was reduced to 64 g/l with an increase in creatinine from 140 to 227 $\mu\text{mol}/l$, urea – up to 29.3 mmol/l, ala-nintransferase – up to 197 U/l. C-reactive protein was significantly increased – 80 $\mu\text{g}/l$, ferritin – 870 $\mu\text{g}/l$, lactate dehydrogenase – 1200 IU/l, blood glucose – 8.2 mmol/l, total cholesterol – 8.43 mmol/l, triglycerides – 3.83 mmol/l. Cooagulogram findings were low PTI – 69.4, fibrinogen level – 1.1 g/l, APTT was 26.6 seconds. with an international normalized ratio of 1.22.

In the preoperative period albumin, tivorel, klexan, insulin were prescribed.

The patient underwent surgery – amputation of the right lower limb in the middle third of the thigh. Results of pathological and histological examination (PHE) of the amputated lower extremity: dermis and adjacent tissues with signs of chronic inflammation. Moderate neutrophilic infiltration. In vessels of a microcirculatory channel – aggregation thrombotic masses without signs of reorganization. In the main artery: atherocalcinosis, intimal hyperplasia, areas of intimal dissection.

The postoperative period passed without complications. The patient was discharged on day 6 for outpatient treatment under the supervision of a family doctor. Patient was prescribed klexan 0.2 subcutaneously, 2 times a day, tivortin. The patient's condition required control of laboratory

findings in 2 weeks with adjustment of further therapy.

Case history 2.

Female patient A., 78 years old, was hospitalized on December 29, 2020 with a diagnosis of atherosclerosis of the vessels of the lower limbs. Thrombosis of the femoral-popliteal segment with ischemia of the right lower limb 4 stage. Secondary diagnoses: ischemic heart disease, diffuse cardio-sclerosis. Heart failure IIA. Functional class II.

On admission to the hospital the patient complained of pain, swelling, blackening of the right foot. The day before the patient had a COVID-19 infection. The result of the analysis for COVID-19 by PCR - negative; antibodies to COVID-19 were determined by enzyme-linked immunosorbent assay: IgG – 8.73 IU/ml, IgM – 0.25 IU/ml.

The patient's condition deteriorated within 2 weeks after infection, so she was admitted to the surgical department of another hospital, where conservative therapy was carried out, including rivaroxaban 15 mg per day for ischemia of the right lower limb, 3-4 stage as a complication of atherosclerotic lesions of the vessels of the lower limbs. Due to the ineffectiveness of conservative therapy and the progression of ischemia, the need for surgical treatment has been determined. Condition on admission of moderate severity. Skin and mucous membranes are moderately pale. At auscultation of lungs the breathing is harsh, in the lower departments – weakened, no wheezing. Heart sounds are dull, rhythmic, blood pressure – 150/90 mm Hg., heart rate – 78 beats/min. The abdomen is soft and painless. The liver and spleen are not enlarged.

Local status: right lower limb is pale, foot up to the ankle joint is of black color. Wound defects up to 3 cm on the lateral surfaces. The edges of the wounds are infiltrated with significant hyperemia. Pulsation in the arteries of the right foot and in the femoral-popliteal segment is not determined. Ischemic tests are positive.

Full blood count: decrease in the level of hemoglobin to 105 g/l, erythrocytes – $3.04 \cdot 10^{12}/l$, thrombocytes – $85 \cdot 10^9/l$, at leukocytosis – $15.4 \cdot 10^9/l$, biochemical findings: total protein – 67 g/l. Particular attention was drawn to the too high levels of D-dimer – 11869 μg FEO/ml, ferritin – 1217 $\mu\text{g}/\text{ml}$, C-reactive protein – 905 $\mu\text{g}/\text{ml}$, lactate dehydrogenase – 1020 IU/l, cholesterol – 7.23 mmol/l, triglycerides – 3.06 mmol/l.

Coagulation disorders were noted: at elevated fibrinogen levels up to 5.5 g/l soluble fibrin monomer complexes were equal to 17 (at reference values of 3.5), which correlated with high levels of D-dimer and low levels of antithrombin 3 – 3.68%.

After preoperative preparation, the patient underwent life-saving surgery on December 30, 2020 – amputation of the right lower limb at the level of the middle third of the thigh.

According to the results of histopathological examination from 12.01.2021:

Artery: atherocalcinosis, intimal hyperplasia, areas of intimal dissection. Vein: in the adjacent great vein – parietal thrombosis with organization, focal endothelial proliferation, capillarization.

Foot: necrosis of the skin and surrounding soft tissues. Along the line of demarcation in the dermis – phenomena of vasculitis, in the fiber – a picture of phlegmonous inflammation. Dermis of the lower third of the tibia: edema of the dermis, perivascular lymphohistiocytic infiltration. Dys-trophic changes in fatty tissue.

The postoperative period was uneventful. The patient was discharged on day 8 after surgery under the supervision of a family doctor with recommendations for the administration of klexan 0.2 subcutaneously 2 times a day, control of coagulogram, ferritin level, D-dimer, C-reactive protein with correction of further therapy.

RESULTS AND DISCUSSION

Both patients had COVID-19, which largely led to the progression of ischemic manifestations of the vessels of the lower limbs in the postcovid period against systemic atherosclerosis. Changes in protein and lipid content with concomitant intoxication impaired renal function, which deepened endotoxemia. Patients received rivaroxaban 15 mg daily (therapeutic dose). Both patients underwent life-saving amputations of the affected limbs. It is established that in COVID-19 infection, especially in patients with vascular lesions, it is necessary to follow the recommendations for anticoagulant therapy with heparin drugs – they inhibit the aggregation properties of platelets and erythrocytes, increase endogenous fibrinolysis, reduce the manifestations of hypoglycemia, do not affect renal function. Due to the effects inherent only in this group of drugs, the development of edema and tissue ischemia was prevented, in contrast to the effect of rivaroxaban

on Xa coagulation factor with inhibition of intravascular coagulation.

According to histological studies, plasma proteins and lipoproteins are involved in the hyaline structure of blood clots. It is known that the cleavage of the latter occurs under the action of lipoprotein lipases which are produced by the endothelium. Heparin increases the activity of lipoprotein lipase which provides a hypolipidemic effect when bound with the capillary wall by proteoglycan chains of heparin sulfate. It is this mechanism that needs to be studied with a probable justification for the benefits of heparin in COVID-19-associated thrombotic complications as compared to anticoagulants with other mechanisms of action.

Determining the risk factors for thrombosis in thrombophilia requires special attention, as there are no randomized studies on evidentiality for anticoagulant therapy, as well as mechanisms of heparin resistance, so the development of algorithms for treatment and prevention of coagulation disorders is a topical issue.

CONCLUSIONS

1. Inasmuch use the mechanisms of thrombosis in COVID-19 are due to a combination of immune inflammation and coagulopathy, the timely appointment of low molecular weight heparins as the most acceptable anticoagulant is optimal for patients at high risk of thrombotic lesions.

2. It is appropriate to develop algorithms for the appointment of low molecular weight heparins in patients with ischemic limb lesions, in particular in COVID-19 infection, with a comprehensive approach to the assessment of clinical and laboratory conditions, taking into account the results of histological examination of amputated limbs, and especially carefully – the state of microcirculation.

3. Further study of clinical cases in patients with thrombotic manifestations, including at the outpatient stage, will allow establishing additional risk criteria of their development with the working off algorithms of treatment and prevention.

Conflict of interests. The authors declare no conflict of interest.

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