https://doi.org/10.25207/1608-6228-2022-29-6-96-106

COVID-19-ASSOCIATED COAGULOPATHY: A CLINICAL CASE

Katsiaryna M. Surmach*, Tatsiana I. Balabanovich, Michail R. Malkin

Grodno State Medical University
M. Gorky str., 80, Grodno 230009, Belarus

ABSTRACT

Background. Comorbid patients with a new coronavirus disease (COVID-19) often have thrombosis or bleeding in different periods of the disease. Early diagnosis of these complications and adequate therapy of these patients are complicated due to the peculiarities of the disease in comorbidity. Anticoagulation regimens in patients with COVID-19 are still unclear. The protocol of efficacy and safety the intermediate or therapeutic dose of low-molecular-weight heparins is not clear and complete. It is very important to organize an individual approach for correction of the anticoagulants doses, taking into account the coagulation tests and the activity of inflammatory markers.

Clinical case description. We report a 71-year-old white male with COVID-19 pneumonia. Acute respiratory distress syndrome and atrial fibrillation were diagnosed in ten days of the disease. Therapeutic anticoagulation was started upon the admission. As early as in the 20th day of the disease a gluteal hematoma developed. Hence, prophylactic regimen of anticoagulation was started, but the worsening of dyspnea at rest, decreasing in SpO2 values to 82% according to pulse oximetry, and thrombelastographic hypercoagulability were observed after two days of such anticoagulation treatment. The patient has been receiving daily low-molecular-weight heparins injections in therapeutic doses for the following two weeks, and then the doctors have switched him to new oral anticoagulants. Patient was discharged to continue ambulatory anticoagulant's treatment.

Conclusion. It is clear that the optimal choice of anticoagulation strategy in comorbid patients with concomitant COVID-19 remains challenging and requires randomized trials. Until the guidelines develop the effective anticoagulation strategy for various phenotypes of COVID-19 patients, the clinicians' knowledge, experience and creative thinking will be apply to choose effective anticoagulant's treatment on individual basis.

Keywords: COVID-19, coagulopathy, thrombosis, hematoma, comorbid patient

Conflict of interest: the authors declare no conflict of interest.

For citation: Surmach K.M., Balabanovich T.I., Malkin M.R. COVID-19-Associated Coagulopathy: a Clinical Case. *Kuban Scientific Medical Bulletin*. 2022; 29(6): 96–106. https://doi.org/10.25207/1608-6228-2022-29-6-96-106

Received 01.06.2022
Adopted after revision 26.08.2022
Published 28.12.2022

COVID-19-АССОЦИИРОВАННАЯ КОАГУЛОПАТИЯ: КЛИНИЧЕСКИЙ СЛУЧАЙ

Е. М. Сурмач*, Т. И. Балабанович, М. Г. Малкин

Учреждение образования «Гродненский государственный медицинский университет»
ул. Максима Горького, д. 80, г. Гродно, 230009, Республика Беларусь

АННОТАЦИЯ

Введение. Течение новой коронавирусной болезни (COVID-19) у пациентов с сопутствующей патологией часто осложняется как тромбозами, так и кровотечениями в разные периоды заболевания. Ранняя диагностика этих осложнений и своевременная адекватная терапия у таких пациентов затруднена в условиях коморбидности. Схемы антикоагулянтной терапии у пациентов с инфекцией, вызванной коронавирусом, до сих пор не до конца ясны. Недостаточно данных о возможности применения профилактических и лечебных доз низкомолекулярных гепаринов. Очень важно рассмотреть принципы индивидуального подхода к коррекции доз антикоагулянтов с учетом результатов коагулограммы и активности маркеров воспаления.

Описание клинического случая. Пациент М., 71 года, поступил в инфекционный стационар с пневмонией, ассоциированной с новым коронавирусом SARS-CoV-2. Через десять дней от начала заболевания развились острый респираторный дистресс-синдром и фибрилляция предсердий. При поступлении в стационар была начата терапия лечебными дозами антикоагулянтов. На 20-й день заболевания развилась межмышечная спонтанная гематома правой ягодичной области. Пациент был переведен на профилактический режим дозирования антикоагулянта, однако через двое суток возникли одышка в покое и снижение значений SpO_2 до 82% по данным пульсоксиметрии, была выявлена гиперкоагуляция по данным тромбоэластограммы. Пациент продолжил лечение низкомолекулярными гепаринами в терапевтических дозах в течение следующих двух недель, а затем был выписан для продолжения амбулаторного лечения, продолжил прием новых пероральных антикоагулянтов.

Заключение. Очевидно, что оптимальный выбор стратегии антикоагулянтной терапии у коморбидных пациентов с сопутствующей коронавирусной инфекцией остается сложной задачей и требует рандомизированных исследований. До тех пор пока не будет разработана эффективная стратегия антикоагулянтной терапии для различных фенотипов пациентов с COVID-19, знания, опыт и творческое мышление врача будут применяться для выбора эффективного лечения антикоагулянтами с учетом персонифицированного подхода.

Ключевые слова: COVID-19, коагулопатия, тромбоз, гематома, коморбидный пациент

Конфликт интересов: авторы заявили об отсутствии конфликта интересов.

Для цитирования: Сурмач Е.М., Балабанович Т.И., Малкин М.Г. COVID-19-ассоциированная коагулопатия: клинический случай. *Кубанский научный медицинский вестник*. 2022; 29(6): 96–106. https://doi.org/10.25207/1608-6228-2022-29-6-96-106

Поступила 01.06.2022
Принята после доработки 26.08.2022
Опубликована 28.12.2022

INTRODUCTION

Studies suggest that thrombosis and bleeding are complications of the novel coronavirus infection. Changes in coagulation tests are found in approximately 50% of patients with COVID-19. T. Jayakrishnan et al. demonstrated that the incidence of thrombotic and bleeding complications is higher among critically ill COVID-19 patients [1, 2]. Many publications propose mechanisms of the coagulopathy. Coronavirus infection can cause activation of the coagulation cascade, fibrinolysis and, in some cases, disseminated intravascular coagulation.

Recent studies determined very high cumulative incidence of thrombotic complications in critically ill patients with COVID-19 pneumonia [3]. Several mechanisms have been considered to cause hypercoagulability in COVID-19 patients including the release of cytokines, causing the production of blood coagulation factors, high levels of fibrinogen, D-dimer, mild thrombocytopenia together with normal values of prothrombin time. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to angiotensin-converting enzyme-2 (ACE-2) receptor found in various pulmonary cells like type II alveolar cells, macrophages, endothelial, smooth muscle cells and perivascular pericytes. These changes cause uncontrolled inflammation, micro-thrombosis of small pulmonary vessels, endothelial dysfunction [4, 5]. The cytokines and especially the interleukin family are known to play an important role in inflammation and have direct effect on the plasma molecules, on erythrocytes and platelets. Hypercoagulability and impaired fibrinolysis are usually the trademarks of several inflammatory conditions [6]. M. Levy et al. showed that COVID-19 coagulopathy mimics disseminated intravascular coagulation or thrombotic microangiopathy. The clinical and laboratory characteristics of the coagulation changes in COVID-19 are variable. Severe COVID-19 infection induce systemic inflammation, hypoxia, severe endothelial cell injury with release of von Willebrand factor and plasminogen activators resulted in coagulation abnormality and pulmonary microvascular thrombosis [7].

The indications for antiplatelet and anticoagulant use are guided by COVID-19 severity [8]. Hemorrhage is less common than thrombosis in patients with severe COVID-19, reaching a hospital mortality of 45.7%. The etiology of bleedings is multi-factorial — secondary to multi-system organ failure, iatrogenic use of anti-coagulants [9]. COVID-19 is associated with severe thrombosis in the early stages of the disease, but also with bleeding between the second and third weeks of the disease, especially in patients receiving therapeutic doses of anticoagulants T. Jayakrishnan et al. demonstrated that half of patients with major bleeding events were either without anticoagulation or only on the thrombo-prophylactic-doses. Meanwhile, two thirds of the major bleeding events occurred in patients receiving therapeutic anticoagulation. Different studies provide evidence that there are no indications for a full dose of anticoagulant in patients without clinical thrombosis, thromboembolism or absence of other standard indications for therapeutic anticoagulation (mechanical valve prosthesis, atrial fibrillation) [2, 10–12].

CASE PRESENTATION

Patient information

The patient M., a 71-year-old white male, was admitted to Grodno Regional Infectious Clinical Hospital on March 5, 2021. He presented to the department with febrile fever, dry cough, and fatigue.

History of present illness. Patient felt chills and dry cough with 5 days before hospitalization. He used paracetamol, 500 mg, 4–6 times during last 5 days, when the temperature was higher than 38 °C. He had one day of mild diarrhea before hospitalization. It was diagnosed COVID-19-associated pneumonia (non-contrast chest CT showed minimal (1–25%) bilateral lung involvement), laboratory-proven by IgG/IgM-based ELISA kit (SARS-CoV-2 “Ig M+”, “IgG-”) on 5 March, 2021.

Due to the fact of persistent febrile fever during 2 days before hospitalization, intensified not productive cough and dyspnea, bad control of blood pressure in spite of quadri-combination hypotensive therapy, admission to Grodno Regional Infectious Clinical Hospital was required in the patient.

The rest of the history: the patient was hypertensive for 30 years with medical treatment (bisoprolol (Concor®, Merck kGaA, Germany), 10 mg/day, perindopril/indapamide (Noliprel® A Bi-forte, Servier, France), 10/2.5 mg/day, amlodipine (Norvasc®, Pfizer, Germany), 10 mg/day). He suffered from diabetes mellitus type 2 and was treated with oral anti-diabetic medication (metformin (Siofor®, Berlin-Chemie Menarini, Germany), 850 mg/day), as well as rosuvastatin (Rosucard®, Zentiva k.s., Czech Republic), 20 mg/day because of dyslipidemia, and acetylsalicylic acid (Polocard®, Polpharma, Poland), 75 mg/day. Patient has hereditary history of arterial hypertension and diabetes mellitus. No bad habits or allergies.

Physical examination

Patient was admitted in moderate state. The color of skin was pink. Body mass index (BMI) was 30.2 kg/m^2 and waist circumference — 110 cm. Body temperature was 39.2 °C. His respiratory rate was 19 breaths/min, the respiration was effective (SpO_2 94–96%) on room air. Auscultation reviled diminished vesicular breath sounds with crackles in the lower lung lobes bilaterally, small amount of the high-pitched wheezes in interscapular space; diminished S_1, accentuated S_2 on aortic valve were revealed. Heart rhythm was irregular (single ventricular extrasystoles were revealed on ECG). Pulse was 93/min. Blood pressure was 180/110 mm Hg.

The primary diagnosis

Community acquired SARS-CoV-2 associated interstitial bilateral pneumonia, not severe. Respira-

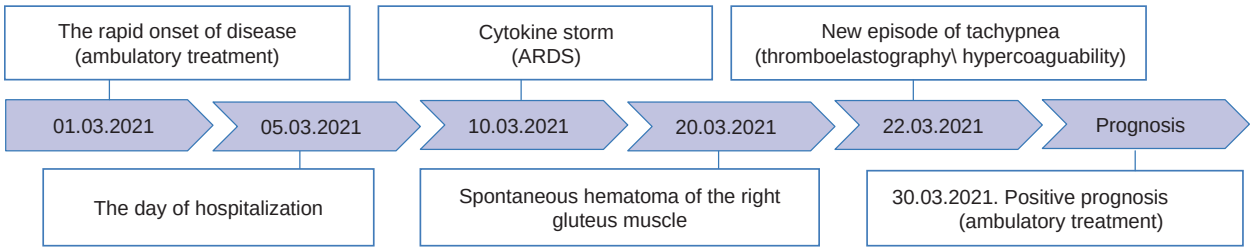

Fig. 1. Sequence of disease in patient M.: key events and prognosis.
Рис. 1. Течение болезни у больного М.: ключевые события и прогноз.

tory failure grade I. Arterial hypertension, grade III, risk 4. Single ventricular extrasystoles. Heart failure: functional class II (NYHA), objective assessment B. Diabetes mellitus type 2, compensation. Obesity grade I (BMI = 30.2 kg/m^2).

The time scale

The chronology of disease is on the Fig. 1.

Diagnostic procedures

Laboratory investigations

Infectious disease testing included evaluation for SARS-CoV-2 using IgG/IgM-based ELISA kit: SARS-CoV-2 "IgM+", "IgG-" (05.03.2021).

Arterial blood gas analysis (05.03.2021) revealed a PaO_2 of 65 mm Hg and a SaO_2 of 94%, moderate hypocapnia.

Complete blood count (CBC) on (05.03.2021) showed red blood cells (RBC) count 5.2×10^{12}/L (normal range 4.0–5.1×10^{12}/L), hemoglobin 153 g/L (normal range 130–160 g/L), hematocrit 44.7% (normal range 34.3–46.6), platelets count 317×10^9/L (normal range 180–320×10^9/L), white blood cells (WBC) count 3.4×10^9/L (normal range 4.0–9.0×10^9/L), neutrophils — 63% (normal range 47–72%), lymphocytes — 21% (normal range 18–40%), erythrocyte sedimentation rate (ESR) 23 mm/h (normal range 1–10 mm/h).

Biochemical test (05.03.2021): total protein 74 g/L (normal range 66–87 g/L), albumin 46 g/L (normal range 38–51 g/L), creatinine 1.14 mg/dL (normal range 0.6–1.1 mg/dL), C-reactive protein (CRP) 24 mg/dL (normal range 0–5 mg/dL), alanine aminotransferase (ALT) 53 U/L (normal range 0–40 U/L), aspartate aminotransferase (AST) 31 U/L (normal range 0–40 U/L), creatine kinase (CK) 116.3 U/L (normal range 24–290 U/L), lactate dehydrogenase (LDH) 386 U/L (normal range 100–250 U/L), glucose 12.9 mmol/L (normal range 3.5–6.2 mmol/L).

Coagulation test (05.03.2022): fibrinogen 616 mg/dL (normal range 200–400 mg/dL), D-dimer 854 ng/mL (normal range less 500 ng/mL).

Instrumental investigations

Non-contrast chest CT (05.03.2022) revealed extensive ground-glass opacification in both lower lobes (minimal (1–25%) bilateral lung involvement).

Electrocardiogram (ECG) (05.03.2021): sinus rhythm, irregular. Heart rate = 93/min. Axis +30°. Single ventricular extrasystoles. Repolarization disturbances in anterior wall of left ventricular.

Electrocardiogram (ECG) (10.03.2021): atrial fibrillation, tachysystolic type. Heart rate = 123/min. Axis +30°. Repolarization disturbances in anterior wall of left ventricle.

Electrocardiogram (ECG) (11.03.2021): sinus rhythm, regular. Heart rate = 88/min. Axis +30°. Repolarization disturbances in anterior wall of left ventricle.

The final clinical diagnosis

Coronavirus infection SARS-CoV-2 IgM "+", IgG "-"(05.03.2021) Community acquired SARS-CoV-2 associated interstitial bilateral pneumonia, not severe. Respiratory failure grade I. Arterial hypertension, grade III, risk 4. Single ventricular extrasystoles. Paroxysmal atrial fibrillation (10.03.2022). Pharmacological cardioversion (11.03.2022). Heart failure: functional class II (NYHA), objective assessment B. Diabetes mellitus type 2, compensation. Obesity grade I (BMI = 30.2 kg/m^2).

Differential Diagnosis

Dyspnea is the most common symptom in patients with coronavirus infection both in the acute period of the disease and in long COVID-19. All the mechanisms of this symptom have not been clarified, however, microthrombosis, destruction of the lungs parenchyma may be the causes of impaired perfusion of lung tissue. A number of authors present clinical reports about different mechanisms of pulmonary hypertension in severe COVID-19, observe a disturbances of lung perfusion within a year after infection. It is the sign of the lung damage, the mechanism of which is not clear [13].

Dyspnea in our case requires a differential diagnosis with many conditions such as pulmonary embolism, complications of pneumonia, including bacterial complications, acute coronary syndrome, and myocarditis in a comorbid patient with acute anemia.

Laboratory and instrumental diagnostic methods can be effective to clarify the causes of shortness of breath: the dynamics of the blood test, D-dimer levels, markers of myocardial damage (creatine kinase MB-fraction (CK-MB), troponin test, myoglobin), B-type natriuretic peptide levels, as well as the results of ECG and Echocardiography. In order to diagnose pulmonary embolism, ventilation-perfusion scanning, duplex ultrasonography, spiral CT can be performed. Today investigators can propose pulmonary dynamic contrast-enhanced magnetic resonance imaging.

We performed laboratory and noninvasive instrumental tests (blood test, levels of procalcitonin, markers of myocardial damage, ECG, echocardiography) and excluded complications such as sepsis, myocarditis and acute coronary syndrome.

Spontaneous gluteus muscle hematoma can be a common symptom of congenital (hemophilia) or acquired coagulation disorders (for example, disseminated intravascular coagulation), may be mistaken for thrombocytopenic purpura or as a manifestation of other cutaneous vasculitis. In addition to these causes anticoagulant or antiplatelet treatment, and also glucocorticosteroids treatment (it may inhibit platelet aggregation and cause spontaneous muscle hematoma) need to be considered by the physicians. It is established, that outside of COVID-19, the incidence of spontaneous hematomas in patients on anticoagulants is 0.6%, but in COVID-19 subjects the frequency of hematomas rise to 2.1% [14].

The spontaneous gluteus muscle hematoma was diagnosed based on ultrasonography (US) appearance: acute bleeds appear as focal areas of high attenuation that, over time, demonstrate decreasing attenuation due to clot lysis. In addition, diffuse parenchymal hemorrhage may present solely as isodense enlargement of the involved gluteus muscle. Our patient had no episodes of hemorrhagic syndrome in the anamnesis and in family history. Also the patient showed normal aPTT, the platelet level was normal essentially excluding hemophilia and thrombocytopenic purpura from the etiology of the spontaneous gluteus muscle hematoma.

Other laboratory tests, including fibrinogen and the D-dimers were found to be abnormal, thereby had possessed a challenge to exclude disseminated intravascular coagulation. The clinical report demonstrates confirmed COVID-19-patient (laboratory-proven by IgG and IgM-based ELISA kit: SARS-CoV-2 “Ig M+”, “IgG-”). The patient’s bleeding tendency (occurrence of spontaneous hematoma) has pathogenic link with this infection and has been explained as possible consequence of imbalances in platelet production/disruption, endothelial dysfunction, coagulopathy, antithrombotic prophylaxis.

Endotelial injury is the sign of COVID-19. Endotelial injury can cause microvascular angiopathy and thrombosis. For the purpose of differential diagnosis (to exclude pulmonary embolism), it was necessary to perform visualization according to the clinical guidelines, however, there was no computed tomographer in the hospital where the patient was treated. The measurement of the risk/ benefit of patient transportation were performed and it was made decision to refuse of visualization. The patient’s dosage of LMWHs was increased, conservative hematoma treatment was continued. The response for treatment was good: we noticed clinical improvement.

Medical interventions

On the day of admission, after the diagnosis was made, the patient was prescribed dexamethasone 8 mg intravenously once daily, subcutaneously prophylactic dose of dalteparinum sodium (Fragmin®, Pfizer, Belgium), 7500 ME, once daily. These were given in addition to the continuation of previous treatment of arterial hypertension and dyslipidemia. Also, initially, the insulin therapy was started. Since at home the patient had febrile temperature for 2 days in spite of high-dose paracetamol therapy, and wheezes were revealed during the auscultation, the decision for dexamethasone prescription was made.

Dynamics and results

Then 4 to 5 days later (the day 9^{th}–10^{th} of disease), the patient developed worsening of respiratory symptoms and laboratory parameters. He became tachypneic (≥30 breaths/min) and presented with PaO_2/FiO_2 ratio ≤300 mm Hg, the oxygen saturation of 86% despite the escalation in non-invasive ventilation (the O_2 flow rate was increased from 5 l/min (the 9^{th} day of the disease) to 15 l/min (the 10^{th} day of the disease)). Blood tests showed progressive growth of CRP, fibrinogen, ferritin (Table 1).

The patient developed hypotension, onset of atrial fibrillation and ventricular extrasystoles at the ECG. The state of patient was assessed as severe; the doctors suspected acute respiratory distress syndrome (ARDS). It was made a decision to administer 400 mg intravenous tocilizumab (Actemra™, Roche, Switzerland). The patient also received amiodarone (Borimed, Belarus) 1000 mg/daily, subcutaneously therapeutic doses (15000 ME) of low-molecu-

Table 1. Laboratory dynamics throughout hospitalization
Таблица 1. Динамика результатов лабораторных исследований во время госпитализации

Laboratory parameters	Reference range	Day of the disease				
		5th	9th	12th	20th–24th	30th
RBC, 10^{12}/L	4.0–5.1	5.2	4.6	5.2	2.8	3.0
Hemoglobin, g/L	130–160	153	136	163	85	89
Hematocrit, %	34.3–46.6	44.7	39.2	47.5	24.6	28.5
Platelets, 10^9/L	180–320	317	210	265	233	279
WBC, 10^9/L	4.0–9.0	3.4	13.7	16.4	15.9	11.0
Neutrophils, band/segmentonuclears, %	1–6/47–72	4/63	4/87	4/90	-/82	15/53
Lymphocytes, %	18–40	21	8	4	16	17
ESR, mm/h	1–10	23	37	51	52/59	52
Total protein,g/L	66–87	74	58	60	45	44
Albumin, g/L	38–51	46	36	33,8	29,4	22
Creatinine, mg/dL,	0.6–1.1	1.14	0.9	1.02	0.75	0.68
GFR, ml/min/1,73 m^2, CKD-EPI	>60	64	85	74	93	97
CRP, mg/L	0–5	24	65	170	35/17	73
ALT/AST, U/L	0–40	53/31	31/29	33/23	21/59	16/28
LDH, U/L	100–250	386	318	651	431	184
Creatine kinase, U/L	24–290	116.3	56.7	25.9	65.9	266
IL-6, pg/mL	0–10	-	103.3	42.7	-	-
Ferritin, ng/mL	30–300	-	817	-	-	-
D-dimer, ng/mL	<500	854	990	-	540	
Fibrinogen, mg/dL	200–400	616	528	440	1300	600
Procalcitonin, ng/mL	<0.5	-	-	-	-	0.8
Glucose, mmol/L	3.5–6.2	12.9	12.7	9.5	8.3	9.9

Note: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GFR, glomerular filtration rate; LDH, lactate dehydrogenase; IL-6, interleukin-6; RBC, red blood cell count; WBC, white blood cell count.
Примечание: ALT — аланин-аминотрансфераза; AST — аспартатаминотрансфераза; CRP — С-реактивный белок; ESR — скорость оседания эритроцитов; GFR — скорость гломерулярной фильтрации; LDH — лактат-дегидрогеназа; IL-6 — интерлейкин-6; RBC — количество эритроцитов; WBC — количество лейкоцитов.

lar-weight heparins (LMWHs). It was prescribed antibacterial treatment. Later, on day 12th of the disease, the patient clinical condition gradually improved with decreasing the O_2 supply to 7 l/min, diminishing of inflammatory biomarkers. ECG showed sinus rhythm. It was noted QTc prolongation (500 msec) requiring canceling of amiodarone and initiation of metoprolol succinate (Betaloc ZOK®, Astrazeneca, Sweden), 200 mg/day orally.

On the 20th day of the disease the patient's oxygen saturation was 97–98% in non-invasive ventilation with a flow rate of O_2 5 l/min, but the patient presented with sudden acute pain in the gluteal region and loss of movement in his right leg. Blood tests showed a reduction in hemoglobin with a drop of its level from 163 g/L to 85 g/L. A surgeon examined the patient. There was a large ecchymosis on the skin of the gluteus and a hard tender mass was palpated. It was diagnosed spontaneous hematoma of the right gluteus muscle (120×150×46 mm, 270 cm^3 confirmed by ultrasound) (Figure 2). The dynamic observation was recommended, and the patient was transferred to a surgical hospital. The dose of LMWHs was decreased to prophylactic (5000 ME) according to the patient's weight and glomerular filtration rate (GFR).

On the 22d day of the disease it was noted progression of dyspnea at rest, the level of saturation decreased to 88–90%, the O_2 flow rate was increased to 10 l/min. Thromboelastography (TEG) was done at the 24th day. The hemostatic condition was defined as hypercoaguable as were noted the following parameters: decreased R-time, tendency of decreasing K-time, increased alpha angle, and increased the maximum amplitude. The coagulation profile, including the TEG is shown in the Table 2.

The TEG revealed that anti-Xa activity was 0,075 IU/mL with a prophylactic reference value of 0.1–0.3 IU/mL. Given the hypercoaguability observed in the patient (Figure 3) the doctors switched him to therapeutic doses of dalteparinum sodium — 10 000 ME.

The patient's condition improved gradually. By the 30th day of the disease: the level of SpO_2 was

Table 2. Coagulation profile including TEG data of the patient
Таблица 2. Коагулограмма пациента, включая показатели ТЭГ

Laboratory parameters	Normal range	Patient's hypercoagulable state
INR	0.85–1.35	1.11
aPTT, s	21.1–36.5	31.3
PT,s	11–16	12.8
Antithrombin III, %	66–124	108
Fibrinogen, mg/dL	200–400	1300
anti-Xa activity, IU/mL	0.1–0.3	0.075
R-time, min	5–10	3.7
K-time, min	1–3	1.3
Alpha angle, degree	53–72	71.3
MA, mm	50–70	70.6
LY30, n (%)	0–8	0.4
CI	–3–3	3.4

Note: aPTT, activated partial thromboplastin time; CI, clotting index; INR, international normalized ratio; K-time, time until clot reaches a fixed strength; MA, maximum amplitude; LY30, lysis at 30 minutes; PT, prothrombin time; R-time, reaction time.
Примечание: aPTT — активированное парциальное тромбопластиновое время; CI — индекс свертывания; INR — международный коэффициент нормализации; K-time — время достижения сгустком фиксированной прочности; MA — максимальная амплитуда; LY30 — лизис через 30 минут; PT — время коагуляции; R-time — время реакции.

94%, off oxygen. The patient was discharged home with specific treatment (metoprolol succinate, 200 mg once daily; perindopril, 10 mg once daily; indapamide, 2.5 mg once daily; spironolactone, 25 mg once daily; amlodipine, 5 mg once daily; rosuvastatin, 20 mg once daily; rivaroxaban, 20 mg once daily; oral iron replacement therapy and folic acid; insulin therapy for diabetes mellitus treatment) with an outpatient follow-up.

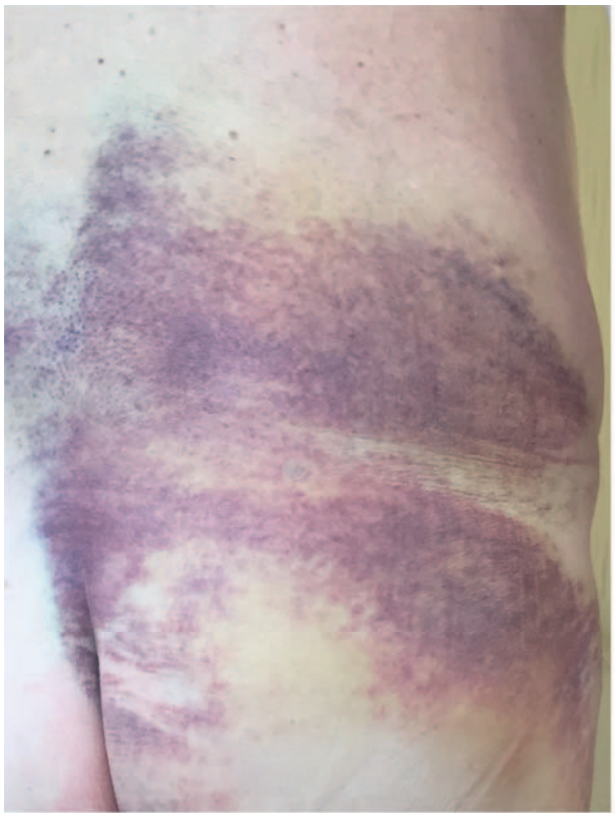

Fig. 2. Hematoma of the right gluteus muscle.
Рис.1. Гематома правой ягодичной мышцы.

Prognosis

Prognosis is positive. Patient M. continues to use all the treatment.

Patient's opinion

Patient thinks that complication of the disease (hematoma) was iatrogenic because of high doses of anticoagulants for treatment.

DISCUSSION

COVID-19 poses a clinical challenge due to the lack of a reliable protocol of anticoagulation therapy. The clinical course of the patient's disease is characterized by stages, which are confirmed by both clinical and laboratory data. Early at the disease course the patient had typical symptoms of viral infection. Symptoms of ARDS, cytokine storm appeared on the 10th day of the disease and were associated with progressive elevation in CRP (up to 170 mg/L), ferritin (up to 817 ng/mL), LDH (up to 651 U/l), IL-6 (up to 103.3 pg/mL), D-dimer (up to 990 ng/mL). Laboratory changes reflected thromboinflammatory processes and were accompanied by a progression of respiratory failure, hypotension, and onset of atrial fibrillation. Clinical and laboratory improvement was noted after the administration of tocilizumab: dyspnea and oxygen demand decreased, IL-6, CRP, D-dimer values decreased. Pharmacological cardioversion was performed. Spontaneous muscle hematoma on therapeutic LMWH for atrial fibrillation appeared. The use of

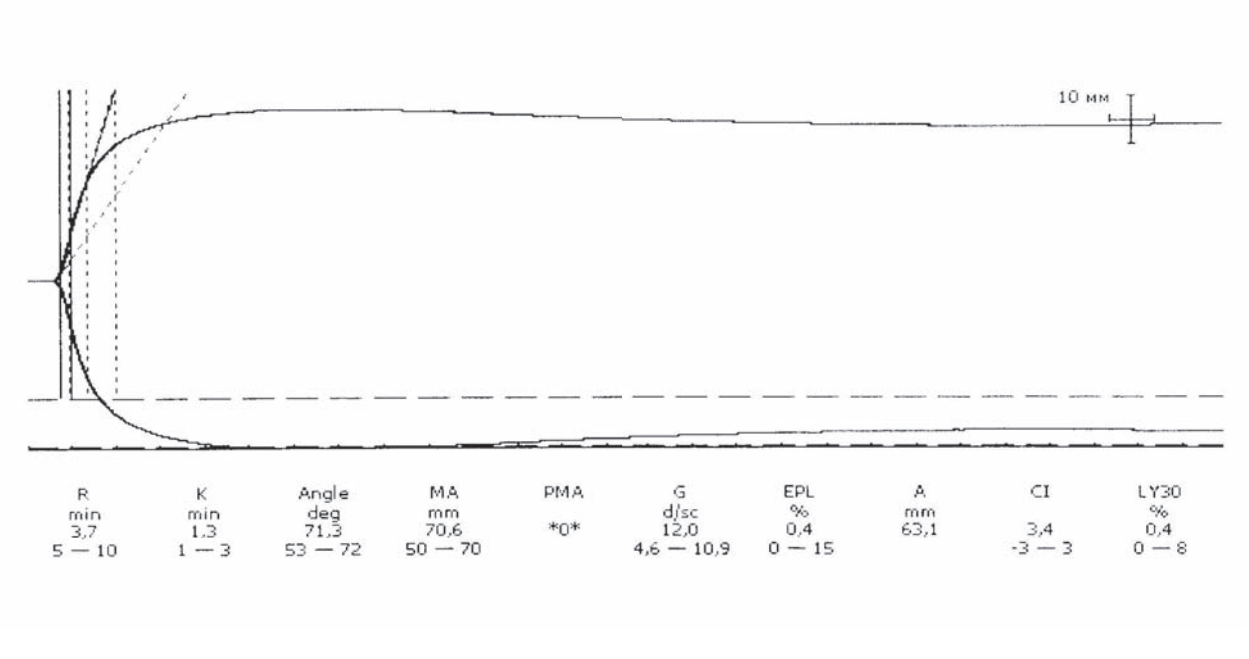

Fig. 3. Thromboelastography (TEG) of the patient: hypercoagulability pattern.
Рис. 3. Показатели тромбоэластографии пациента (TEG): гиперкоагуляция.

therapeutic-dose LMWH manifested as a hematoma of the right gluteus muscle on the 3^{d} week of the disease. Such bleeding complication seems probable to be influenced by COVID-19 coagulopathy and vasculopathy. To date, none personalized treatment anticoagulant regimes are developed in COVID-19 patients.

N.Musoke et al. investigated the bleeding rates in patients (*n* = 355) with therapeutic, subtherapeutic and prophylactic doses of anticoagulation. Patients who received therapeutic anticoagulation treatment showed significantly higher rates of major bleeding. Meanwhile, subtherapeutic dose of anticoagulation was associated with less bleeding compared to therapeutic regimen but the bleeding risk was higher compared to those without anticoagulation [12]. Analysis of anti-Xa activity may be useful for assessing the risk of unpredictable bleeding in patients receiving anticoagulants. Fibrinogen may be a useful biomarker for early detection of bleeding risk [15–17].

Endotelial injury is the sign of COVID-19. Endotelial injury can cause microvascular angiopathy and thrombosis. For the purpose of differential diagnosis (to exclude pulmonary embolism), it was necessary to perform visualization according to the clinical guidelines, however, there was no computed tomographer in the hospital where the patient was treated. The measurement of the risk/ benefit of patient transportation were performed and it was made decision to refuse of visualization. The patient's dosage of LMWHs was increased, conservative hematoma treatment was continued. The response for treatment was good: we noticed clinical improvement.

CONCLUSION

The optimal type, dose, duration and time of anticoagulant use have not yet been determined in literature. In this clinical case assessment of the bleeding risk and the risk of thrombotic events were made to prescribe adequate therapeutic doses of anticoagulants. Of particular importance is the progression of respiratory failure with an increase in oxygen support after the changes of anticoagulants doses. Low anti-factor Xa (anti-Xa) activity was the indication for therapeutic anticoagulation that improved the patient's saturation. Thromboprophylaxis should be adapted to the two-phases of COVID-19 with an individual assessment of the risk of bleeding / thrombosis for each patient (taking into account the dynamics of BMI, GFR; it is advisable to recalculate the dose of anticoagulant). After the inflammatory phase with high prothrombotic risk, the second phase of bleeding risk is coming with diminished levels of D-dimer and fibrinogen. Evidently, the one-size-fits-all approach to anticoagulation will not work for COVID-19 patients. True medical mastery must be forged in the management of such patients.

INFORMED CONSENT

The patient provided a free written informed consent for the clinical case description and photograph publication in a medical journal, including its electronic version signed (15.05.2022).

ИНФОРМИРОВАННОЕ СОГЛАСИЕ

От пациента получено письменное информированное добровольное согласие на публикацию описания клинического случая и публикацию фотоматериалов в медицинском журнале, включая его электронную версию (дата подписания — 15.05.2022).

FUNDING

The authors declare that no funding was received for this study.

ИСТОЧНИК ФИНАНСИРОВАНИЯ

Авторы заявляют об отсутствии спонсорской поддержки при проведении исследования.

REFERENCES / СПИСОК ЛИТЕРАТУРЫ

1. Miesbach W., Makris M. COVID-19: Coagulopathy, Risk of Thrombosis, and the Rationale for Anticoagulation. *Clin. Appl. Thromb. Hemost*. 2020; 26: 1076029620938149. DOI: 10.1177/1076029620938149
2. Jayakrishnan T., Haag A., Mealy S., Minich C., Attah A., Turk M., Alrifai N., Alhuneafat L., Khoury F., Nasrullah A., Wedgeworth P., Mosley M., Vashistha K., Bakalov V., Chaturvedi A., Sangli S. Novel Coronavirus Infection (COVID-19) Related Thrombotic and Bleeding Complications in Critically Ill Patients: Experience from an Academic Medical Center. *J. Clin. Med*. 2021; 10(23): 5652. DOI: 10.3390/jcm10235652
3. Klok F.A., Kruip M.J.H.A., van der Meer N.J.M., Arbous M.S., Gommers D., Kant K.M., Kaptein F.H.J., van Paassen J., Stals M.A.M., Huisman M.V., Endeman H. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thromb. Res*. 2020; 191: 148–150. DOI: 10.1016/j.thromres.2020.04.041
4. Hanff T.C., Mohareb A.M., Giri J., Cohen J.B., Chirinos J.A. Thrombosis in COVID-19. *Am. J. Hematol*. 2020; 95(12): 1578–1589. DOI: 10.1002/ajh.25982
5. Huertas A., Montani D., Savale L., Pichon J., Tu L., Parent F., Guignabert C., Humbert M. Endothelial cell dysfunction: a major player in SARS-CoV-2 infection (COVID-19)? *Eur. Respir. J.* 2020; 56(1): 2001634. DOI: 10.1183/13993003.01634-2020
6. Rabaan A.A., Al-Ahmed S.H., Muhammad J., Khan A., Sule A.A., Tirupathi R., Mutair A.A., Alhumaid S., Al-Omari A., Dhawan M., Tiwari R., Sharun K., Mohapatra R.K., Mitra S., Bilal M., Alyami S.A., Emran T.B., Moni M.A., Dhama K. Role of Inflammatory Cytokines in COVID-19 Patients: A Review on Molecular Mechanisms, Immune Functions, Immunopathology and Immunomodulatory Drugs to Counter Cytokine Storm. *Vaccines (Basel)*. 2021; 9(5): 436. DOI: 10.3390/vaccines9050436
7. Levi M. COVID-19 coagulopathy vs disseminated intravascular coagulation. *Blood Adv*. 2020; 4(12): 2850. DOI: 10.1182/bloodadvances.2020002197
8. Godino C., Scotti A., Maugeri N., Mancini N., Fominskiy E., Margonato A., Landoni G. Antithrombotic therapy in patients with COVID-19? Rationale and Evidence. *Int. J. Cardiol*. 2021; 324: 261–266. DOI: 10.1016/j.ijcard.2020.09.064
9. Altschul D.J., Unda S.R., de La Garza Ramos R., Zampolin R., Benton J., Holland R., Fortunel A., Haranhalli N. Hemorrhagic presentations of COVID-19: Risk factors for mortality. *Clin. Neurol. Neurosurg*. 2020; 198: 106112. DOI: 10.1016/j.clineuro.2020.106112
10. Rogani S., Calsolaro V., Franchi R., Calabrese A.M., Okoye C., Monzani F. Spontaneous muscle hematoma in older patients with COVID-19: two case reports and literature review. *BMC Geriatr*. 2020; 20(1): 539. DOI: 10.1186/s12877-020-01963-4
11. Castro R.A., Frishman W.H. Thrombotic Complications of COVID-19 Infection: A Review. *Cardiol. Rev*. 2021; 29(1): 43–47. DOI: 10.1097/CRD.0000000000000347
12. Musoke N., Lo K.B., Albano J., Peterson E., Bhargav R., Gul F., DeJoy R. 3rd, Salacup G., Pelayo J., Tipparaju P., Azmaiparashvili Z., Patarroyo-Aponte G., Rangaswami J. Anticoagulation and bleeding risk in patients with COVID-19. *Thromb. Res*. 2020; 196: 227–230. DOI: 10.1016/j.thromres.2020.08.035
13. Yu J.Z., Granberg T., Shams R., Petersson S., Sköld M., Nyrén S., Lundberg J. Lung perfusion disturbances in nonhospitalized post-COVID with dyspnea-A magnetic resonance imaging feasibility study. *J. Intern. Med*. 2022; 292(6): 941–956. DOI: 10.1111/joim.13558
14. Abate V., Casoria A., Rendina D., Muscariello R., Nuzzo V., Vargas M., Servillo G., Venetucci P., Conca P., Tufano A., Galletti F., Di Minno G. Spontaneous Muscle Hematoma in Patients with COVID-19: A Systematic Literature Review with Description of an Additional Case Series. *Semin. Thromb. Hemost.* 2022; 48(1): 100–108. DOI: 10.1055/s-0041-1732370
15. Nadkarni G.N., Lala A., Bagiella E., Chang H.L., Moreno P.R., Pujadas E., Arvind V., Bose S., Charney A.W., Chen M.D., Cordon-Cardo C., Dunn A.S., Farkouh M.E., Glicksberg B.S., Kia A., Kohli-Seth R., Levin M.A., Timsina P., Zhao S., Fayad Z.A., Fuster V. Anticoagulation, Bleeding, Mortality, and Pathology in Hospitalized Patients With COVID-19. *J. Am. Coll. Cardiol*. 2020; 76(16): 1815–1826. DOI: 10.1016/j.jacc.2020.08.041
16. Boira I., Esteban V., Vañes S., Castelló C., Celis C., Chiner E. Major Bleeding Complications in COVID-19 Patients. *Cureus*. 2021; 13(8): e16816. DOI: 10.7759/cureus.16816
17. Sholzberg M., Tang G.H., Negri E., Rahhal H., Kreuziger L.B., Pompilio C.E., James P., Fralick M., AlHamzah M., Alomran F., Tseng E., Lim G., Lilli-

crap D., Carrier M., Áinle F.N., Beckett A., da Costa B.R., Thorpe K., Middeldorp S., Lee A., Cushman M., Jüni P. Coagulopathy of hospitalised COVID-19: A Pragmatic Randomised Controlled Trial of Therapeutic Anticoagulation versus Standard Care as a Rapid Response to the COVID-19 Pandemic (RAPID COVID COAG — RAPID Trial): A structured summary of a study protocol for a randomised controlled trial. *Trials*. 2021; 22(1): 202. DOI: 10.1186/s13063-021-05076-0

AUTHOR CONTRIBUTIONS

Surmach K.M.

Conceptualization — concept statement; development of key goals and objectives.

Conducting research — patient follow-up, data analysis and interpretation.

Text preparation and editing — drafting of the manuscript and its final version, contribution to the scientific layout.

Approval of the final manuscript — acceptance of responsibility for all types of the work, integrity of all parts of the paper and its final version.

Balabanovich T.I.

Conceptualization — development of key goals and objectives.

Conducting research — data analysis and interpretation.

Text preparation and editing — critical review of the manuscript draft with the introduction of valuable intellectual content; contribution to the scientific layout.

Approval of the final manuscript — acceptance of responsibility for all types of the work, integrity of all parts of the paper and its final version.

Malkin M.G.

Conceptualization — concept statement.

Conducting research — data collection.

Text preparation and editing — critical review of the manuscript draft with the introduction of valuable intellectual content; contribution to the scientific layout.

Approval of the final manuscript — acceptance of responsibility for all types of the work, integrity of all parts of the paper and its final version.

ВКЛАД АВТОРОВ

Сурмач Е.М.

Разработка концепции — формирование идеи, развитие ключевых целей и задач.

Проведение исследования — наблюдение за пациентом, интерпретация анализ полученных данных.

Подготовка и редактирование текста — составление черновика рукописи и формирование его окончательного варианта, участие в научном дизайне.

Утверждение окончательного варианта — принятие ответственности за все аспекты работы, целостность всех частей статьи и ее окончательный вариант.

Балабанович Т.И.

Разработка концепции — развитие ключевых целей и задач.

Проведение исследования — интерпретация анализ полученных данных.

Подготовка и редактирование текста — критический пересмотр черновика рукописи с внесением ценного интеллектуального содержания; участие в научном дизайне.

Утверждение окончательного варианта — принятие ответственности за все аспекты работы, целостность всех частей статьи и ее окончательный вариант.

Малкин М.Г.

Разработка концепции — формирование идеи.

Проведение исследования — сбор данных.

Подготовка и редактирование текста — критический пересмотр черновика рукописи с внесением ценного интеллектуального содержания; участие в научном дизайне.

Утверждение окончательного варианта — принятие ответственности за все аспекты работы, целостность всех частей статьи и ее окончательный вариант.

INFORMATION ABOUT THE AUTHORS / СВЕДЕНИЯ ОБ АВТОРАХ

Katsiaryna M. Surmach* — Cand. Sci. (Med.), Assoc. Prof., Department of Propaedeutics of Internal Diseases, Grodno State Medical University.

https://orcid.org/0000-0001-8902-8533

Contact information: e-mail: esurmach@mail.ru;

Maxim Gorky str., 80, Grodno, 230009, Belarus

Tatsiana I. Balabanovich — Cand. Sci. (Med.), Assistant, 1st Department of Internal Diseases, Grodno State Medical University.

https://orcid.org/0000-0002-5552-8764

Michail R. Malkin — Assistant, Department of Traumatology, Orthopedics and Military Field Surgery, Grodno State Medical University.

https://orcid.org/0000-0001-8816-8649

Сурмач Екатерина Михайловна* — кандидат медицинских наук, доцент, доцент кафедры пропедевтики внутренних болезней учреждения образования «Гродненский государственный медицинский университет».

https://orcid.org/0000-0001-8902-8533

Контактная информация: e-mail: esurmach@mail.ru;

ул. Максима Горького, д.80, г. Гродно, 230009, Республика Беларусь

Балабанович Татьяна Игоревна — кандидат медицинских наук, ассистент 1-й кафедры внутренних болезней учреждения образования «Гродненский государственный медицинский университет».

https://orcid.org/0000-0002-5552-8764

Малкин Михаил Григорьевич — ассистент кафедры травматологии, ортопедии и ВПХ учреждения образования «Гродненский государственный медицинский университет».

https://orcid.org/0000-0001-8816-8649

* Автор, ответственный за переписку / Corresponding author