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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Retroperitoneal hematoma – an unexpected complication of anticoagulant therapy in COVID-19 patients

Igor Vasković[1], Ivo Udovičić[1], Mihailo Stojić[1], Ljiljana Arsenović[2], Vojislava Nešković[1]

[1]Military Medical Academy, Clinic for Anesthesiology and Intensive Care, Belgrade, Serbia;
[2]Military Medical Academy, Institute for Medical Biochemistry, Belgrade, Serbia

SUMMARY

Introduction Coronavirus disease 2019 (COVID-19) is associated with high inflammatory response, hemostatic disturbances, and high thrombotic risk. Despite thromboprophylaxis, a high incidence of thromboembolic events has been reported with a consequent increase in anticoagulant therapy from standard to intermediate or even therapeutic doses. However, published evidence on the incidence and outcome of the hemorrhagic complications of applied therapy is still limited.

Outlines of cases We present two female COVID-19 patients, treated with anticoagulant therapy who suffered from major spontaneous bleeding and retroperitoneal hematoma. The first, a 64-year-old patient, treated with non-invasive ventilation protocol in the Intensive Care Unit due to respiratory failure received a therapeutic dose of anticoagulant therapy adjusted to the anti-Xa assay. The cumulative dose of nadroparin was 150 IU/kg body weight/day. The second, a 60-year-old patient with the moderate clinical presentation on low flow oxygen support was treated with therapeutic doses of anticoagulant therapy calculated according to the body weight. Emergency open surgery was performed due to massive bleeding. No active surgical bleeding was detected, and retroperitoneal hematomas were assumed to be complications of the applied anticoagulant therapy. Both patients were discharged and fully recovered.

Conclusion Although rare, severe hemorrhage requires attention when considering anticoagulant therapy in COVID-19. Uncommon sites of spontaneous bleeding suggest additional evaluation on a case-by-case basis, given that a diagnosis is often delayed due to a lack of specific presenting symptoms. Further studies are needed to verify the risk-benefit ratio of different regiments of anticoagulant therapy in patients with COVID-19.

Keywords: COVID-19; anticoagulants; hemorrhage; retroperitoneal space

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a systemic disease characterized by immune system hyperactivity, endothelial dysfunction, and hemostasis disorders. Hemostasis disorders are one of the critical aspects of the pathophysiology of this disease, and various mechanisms such as cytokine storm, antiphospholipid syndrome, activation of macrophages and complement cascades are related to them [1]. All these derangements significantly increase the risk of thrombosis, and 20–30% of critically ill COVID-19 patients develop pulmonary thromboembolism and deep vein thrombosis [2]. On the other hand, studies published before the pandemic showed that 8–10% of patients in the Intensive Care Unit (ICU) develop thromboembolic complications regardless of prophylactic doses of anticoagulant therapy [3].

The high incidence of thrombosis in patients with COVID-19 made some clinicians increase the dose of anticoagulant therapy from prophylactic to intermediate or therapeutic doses. However, the efficacy and safety of various anticoagulant therapy protocols are still lacking [4]. Most of the published clinical trials have focused on thromboembolic complications, while the risk factors and frequency of bleeding, and its impact on patient morbidity and mortality, remain unknown.

Here we present two female COVID-19 patients, treated with anticoagulant therapy and suffering from major spontaneous bleeding and retroperitoneal hematoma. Our research database covered the period from April 2020 to December 2021 in Karaburma COVID Hospital.

REPORTS OF CASES

Case 1

A 64-year-old woman, a long-term hypertensive patient on regular therapy, obese (body weight 90 kg, body height 175 cm), and unvaccinated, was transferred from the ward of our hospital to the ICU due to respiratory insufficiency. At the time of her deterioration, she had oxygen support with a non-rebreather mask (NRM) with a flow rate of 15 l/min. She was dyspneic, with paroxysmal coughing fits, tachypneic with a respiratory rate up to 35/min, with oxygen saturation (SpO_2) of 89–92%. Immediately after admission, non-invasive ventilation was started, with the following

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Correspondence to:
Igor VASKOVIĆ
Military Medical Academy
Clinic for Anesthesiology and Intensive Care
Crnotravska 17
11000 Belgrade
Serbia
vaske79@gmail.com

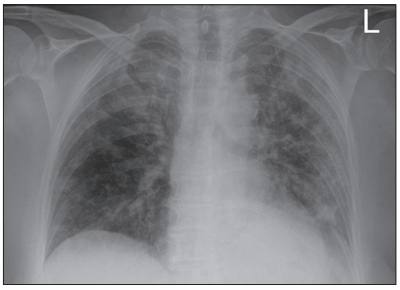

Figure 1. Case 1 – chest radiograph shows bilateral patchy pulmonary consolidations

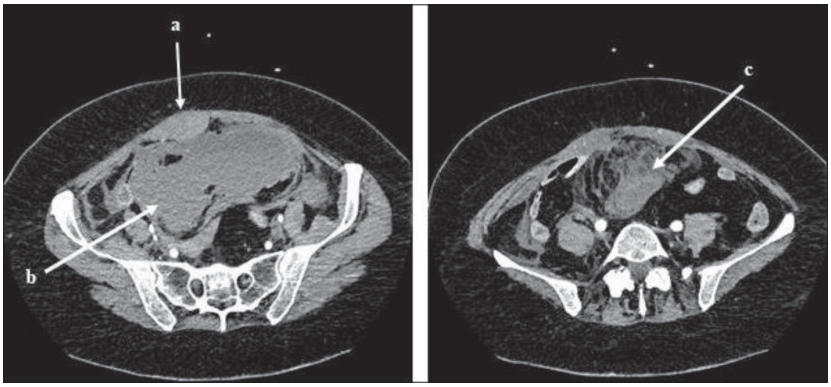

Figure 2. Case 1 – (a) axial computed tomography scans of the abdomen and pelvis show right rectus abdominis muscle hematoma (b) extending into the extraperitoneal pelvis; (c) hemorrhagic collection posterior to the anterior abdominal wall

Table 1. Case 1 – blood tests during the intensive care unit course

Data	Hgb g/l	Plt 10^9/l	Urea mmol/l	Cre mmol/l	GFR ml/min/ 1.73 m^2	CRP mg/l	IL6 pg/ ml	INR	Fib g/l	Dd mg/l	AT III U/ml	Axa U/ml
Normal range	115–165	140–450	2.5–7.5	44–88	≥ 90	0–5		0.7–1.2	2–4	0–0.5	0.8–1.2	
Day 1	137	246	9.1	56	101	18.1	19.6	0.92		2.13		
Day 3	125	291	9.0	44	107	169.3	576	1.04	6.2	3.02	0.94	0.50
Day 5	129	252	7.1	47	106	61.4			4.9	3.80		
Day 7	143	394	6.3	50	104	8.7				6.38		
Day 8								1.01	2.5	3.71	0.85	1.07
Day11	134	342	6.1	45	107	2.1				1.69		
Day 14	135	251	6.2	49	105	0.7				0.91		
Day 15	108	259	8.5	44	107	0.5		1.07		0.64		

Hgb – hemoglobin; Plt – platelets; Cre – creatinine; GFR – glomerular filtration rate; CRP – C-reactive protein; IL6 – interleukin 6; INR – international normalized ratio; Fib – fibrinogen; Dd – D-dimer; AT III – antithrombin III; AXa – anti Xa assay (therapeutic range 0.5–1 U/ml, prophylaxis range 0.1–0.4 U/ml)

parameters: FiO_2 80%, positive end-expiratory pressure (PEEP) 8 cmH_2O, Pasb 0, whereby the respiratory frequency decreased to 25/min with SpO_2 of 96–97%. Her initial X-rays showed bilateral patchy pulmonary infiltrates (Figure 1). Twelve hours after admission, and after measurement of arterial blood gas test (pH 7.46, $PaCO_2$ 33 mmHg, PaO_2 170 mmHg, HCO_3 23.5 mmol/l, BE 0.2 mmol/l, lactate 1 mmol/l), respiratory parameters were corrected to FiO_2 60%, PEEP 6 cmH_2O, Pasb 0.

Low molecular weight heparin was dosed according to the local algorithm of the hospital: Nadroparin 0.6 ml subcutaneously, once a day for patients up to 100 kg or 0.9 ml subcutaneously, once a day for patients over 100 kg, if the D-dimer values were < 2 mg/L fibrinogen equivalent units; while for patients with D-dimer > 2 mg/L fibrinogen equivalent units, an adequate dose (relative to body weight) of low molecular weight heparin was given twice a day. Thus, an initial intermediate dose of anticoagulant therapy was started with Nadroparin 0.6 ml, subcutaneously, twice daily. After four doses of nadroparin, on the third day and four hours after the morning dose, an anti-Xa test was performed together with other hemostasis parameters (Table 1). After obtaining the anti-Xa test (0.5 U/ml), anticoagulant therapy was corrected (nadroparin 0.6 ml + 0.9 ml) so that the cumulative dose of 150 U/kg body weight/day was reached. After dose adjustment, according to the same regimen, the patient's hemostatic profile was repeated on the eighth day when the anti-Xa test value was assumed satisfactory (1.07 U/ml) (Table 1).

On the third day, after checking the blood investigation, Tocilizumab was prescribed according to the drug administration protocol due to further deterioration (Table 1).

In the next few days, the patient improved, and the values of the inflammatory parameters decreased (Table 1). On day 10, her oxygen support switched from non-invasive ventilation to a NRM, with a gradual reduction in oxygen flow over the next few days.

On day 15, the patient complained of lower abdominal pain in the morning. In the afternoon, the pain became more intense with abdominal tenderness and minimal distention. She became hypotensive and tachycardic. The laboratory tests revealed a decrease in hemoglobin level to 108 mg/l (Table 1). She had oxygen support with NRM 15 l/min, and arterial blood gas test showed PaO_2 192 mmHg, $PaCO_2$ 31 mmHg, HCO_3 23.1, BE 0.2, lactates 3.1.

Due to the hospital's limited resources, the patient was transferred to another hospital for further diagnosis and treatment under suspicion of severe bleeding. The patient underwent an urgent medial laparotomy with the dominant finding of the right rectus abdominis muscle's hematoma and bilateral retroperitoneal bleeding. Approximately 1300 ml of blood with coagula were evacuated (Figure 2). The postoperative course was uneventful, and the patient was discharged from the hospital in a good general condition.

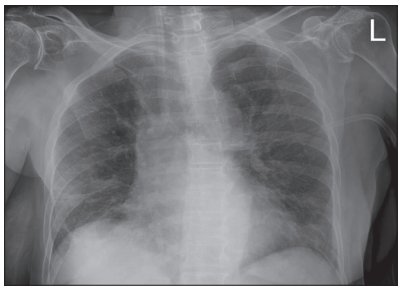

Figure 3. Case 2 – chest X-ray scan shows extensive bilateral pulmonary consolidations involving both lower lobes with a zone of reduced pericardial transparency of the left lung

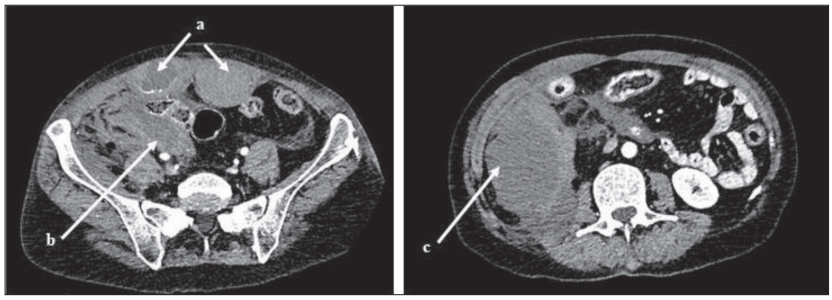

Figure 4. Case 2 – (a) axial computed tomography scans of the abdomen and pelvis show bilateral rectus abdominis muscles hematomas (b) extending into the extraperitoneal pelvis; another hemorrhagic collection in the right retroperitoneum with displaced adjacent structures (c)

Table 2. Case 2 – blood tests during the hospital course

Data	Hgb (g/l)	Plt 10^9/l	Urea (mmol/l)	Cre (mmol/l)	GFR ml/min/1.73 m^2	CRP (mg/l)	IL6 (pg/ml)	INR	Dd (mg/l)
Normal range	115–165	140–450	2.5–7.5	44–88	≥ 90	0–5			0–0.5
Day 1	144	162	5.0	66	90	18.1			0.41
Day 2	133	293	7.5	61	97	74.3	75.4		0.52
Day 6	134	337	6.6	56	99	73.0			0.73
Day 8	145	493	8.9	63	95	18.8			1.86
Day 13	136	362	8.5	53	101	1.2			0.83
Day 16	130	304	7.1	54	100	0.4		0.97	0.65

Hgb – hemoglobin; Plt – platelets; Cre – creatinine; GFR – glomerular filtration rate; CRP – C-reactive protein; IL6 – interleukin 6; INR – international normalized ratio; Dd – D-dimer

Case 2

A 60-year-old obese woman (body weight 70 kg, body height 157 cm), vaccinated, with rheumatoid arthritis, after the triage in the COVID Center in Belgrade, she was admitted to the ward of our hospital for further treatment of proven SARS-CoV-2 infection and consequential bilateral pneumonia. The disease began 10 days before admission with the appearance of cough, malaise, shortness of breath, and fever. Immediately after admission, supportive oxygen therapy was initiated using a nasal catheter with a flow rate of 2 l/min, achieving SpO_2 of 96–97%. The initial chest X-ray showed extensive bilateral pulmonary infiltrates involving both lower lobes with a zone of reduced paracardial transparency of the left lung (Figure 3).

Prophylactic thromboprophylaxis was started with nadroparin 0.6 ml, subcutaneously, once daily according to the local algorithm. In the next few days, the patient's condition worsened with a progressive increase in oxygen support. After checking laboratory results on the fifth hospital day, tocilizumab was prescribed according to the drug dosage information (Table 2). On the eighth day, due to further progression of the disease, oxygen support was increased to NRM with a flow rate of 15 l/min. The therapeutic dose of anticoagulant therapy was started according to the patient's body weight, with nadroparin 0.6 ml twice a day.

In the next few days, the patient improved with a decrease in inflammatory parameters (Table 2) and a gradual decrease of oxygen support to the nasal catheter at a flow rate of 2 l/min.

On day 16 after admission, the patient complained of abdominal pain. The abdomen was painfully sensitive to light and deep palpation during the physical examination, particularly in the ileocecal and suprapubic regions. Urine retention was assumed, but 100 ml of clear urine was obtained after the urinary catheter placement. The laboratory tests revealed a slight decrease in hemoglobin level compared to the previous result, but still within the normal range (Table 2). The patient became hypotensive and tachycardic, and because of suspicion of acute abdomen and bleeding as a complication of anticoagulant therapy, she was urgently transported to the surgical facility of another COVID hospital.

Abdominal and pelvic computed tomography scans showed hematomas of rectus abdominis muscles, 42 × 56 × 110 mm on the left and 40 × 55 × 120 mm on the right side. There were also two hemorrhagic collections: in the right pelvis with a diameter of 60 × 90 mm, which pushes the central pelvic organs contralaterally, and in the right retroperitoneum with a size of 80 × 110 mm, which luxates the ascending colon and pushes the right kidney to the anterior abdominal wall (Figure 4). The patient underwent emergency surgery when around 3000 ml of blood with coagula was evacuated. The postoperative course went well, and the patient was discharged from the hospital in a good general condition.

Data from the database of the doctoral dissertation "Hemostatic profile and effectiveness of anticoagulant therapy in patients with acute respiratory failure in COVID-19" was used, which was approved by the Ethics Committee of the Military Medical Academy on May 25, 2022.

DISCUSSION

All anticoagulation guidelines in COVID-19 suggest thromboprophylaxis for hospitalized patients [5]. Three large international clinical trials published last year, collectively called multiplatform randomized controlled trials, described the effects of different dose regimens of heparin in both non-critically and critically ill patients [6, 7]. The primary outcome was a combination of hospital mortality and organ support-free days at 21 days in non-critically ill patients or patients in the ICU (critically ill). The results showed that therapeutic anticoagulation did not improve outcomes or mortality in the critically ill (including patients receiving high-flow oxygen). Opposite to this, in patients with moderate COVID-19 and low flow oxygen support, therapeutic anticoagulation reduced the need for organ support. Although low, the incidence of bleeding was higher with therapeutic anticoagulation than with usual thromboprophylaxis in both groups of patients [6, 7]. In ICU patients, major bleeding occurred in 3.8% of the patients assigned to receive therapeutic-dose anticoagulation and 2.3% of those assigned to receive usual-care thromboprophylaxis [6]. In non-critically ill patients, major bleeding occurred in 22 of 1180 patients (1.9%) in the therapeutic-dose anticoagulation group and nine of 1047 (0.9%) in the usual-care thromboprophylaxis group. Fatal bleeding occurred in three patients in the anticoagulation group and one in the thromboprophylaxis group [7]. Our first patient was critically ill with high-flow oxygen support and a therapeutic dose of anticoagulant therapy adjusted to anti-Xa assay; the second was moderately ill on low-flow oxygen and therapeutic doses of anticoagulation calculated according to the body weight. Although current guidelines recommend a prophylactic anticoagulation for adults who require ICU-level care, including those receiving high-flow oxygen, and a therapeutic dose of anticoagulation for patients who require low-flow oxygen, both of our patients had significant bleeding as a complication of therapeutic anticoagulation therapy [8]. Moreover, they had a spontaneous retroperitoneal hematoma (SRH), an unusual and uncommon complication of anticoagulants [9].

SRH is challenging to diagnose because of the vague signs and symptoms. Patients with retroperitoneal bleeding have very subtle clinical signs of hemorrhage. Very discreet hemodynamic instability, mild hypotension and tachycardia that improve with intravenous fluids for a short period should raise the clinician's suspicion about possible retroperitoneal hematoma and further investigation [10]. It is believed that the term spontaneous means the absence of specific underlying pathology or trauma; many data implied that unrecognized, minor injuries such as vomiting or coughing can cause minor bleeding that can be promoted and augmented with anticoagulation therapy. In a small study with 12 patients, anticoagulation therapy was the reason for large hematoma of the rectus abdominis muscle; six of them had a history of coughing attacks [11]. This may be a plausible explanation of our patients' rectus abdominis muscle hematomas and retroperitoneal bleeding mechanism, considering the low bleeding risk of our patients in view of the lack of other comorbidities such as renal disease or any bleeding disorders.

SRH is usually associated with anticoagulant therapy, bleeding disorders, and hemodialysis patients [12]. Recently, spontaneous retroperitoneal bleeding with massive deep vein thrombosis has been reported in a patient with COVID-19 who was not even on anticoagulant therapy, without any history of bleeding diathesis or trauma prior to admission to the hospital [13]. This case emphasizes that the COVID-19 induced procoagulant state can cause massive thrombosis and the need for therapeutic doses of anticoagulation. However, the risk of hemorrhagic complications should always be considered, with caution regarding dose regimens of anticoagulant therapy in specific patients.

It is very delicate to keep the equilibrium between anticoagulant therapy, and thrombotic and hemorrhagic complications in patients with COVID-19. Hence, the optimal anticoagulation protocol is still debatable. Retroperitoneal hematoma, an uncommon site of spontaneous bleeding, is a rare complication of anticoagulants. Additional evaluation on a case-by-case basis is needed in light of the absence of specific presenting symptoms and delayed diagnosis. Further studies are needed to verify the risk-benefit ratio of different regiments of anticoagulant therapy in patients with COVID-19.

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Ретроперитонеални хематом – неуобичајена компликација антикоагулантне терапије код болесника са ковидом 19

Игор Васковић[1], Иво Удовичић[1], Михаило Стојић[1], Љиљана Арсеновић[2], Војислава Нешковић[1]

[1]Војномедицинска академија, Клиника за анестезиологију и интензивну терапију, Београд, Србија;
[2]Војномедицинска академија, Институт за медицинску биохемију, Београд, Србија

САЖЕТАК

Увод Болест изазвана вирусом корона (ковид 19) карактерише се хиперинфламаторним одговором, хемостатским поремећајима и високим ризиком од тромбозе. Упркос тромбопрофилакси, бројне студије су показале високу инциденцију тромбоемболијских догађаја са последичним повећањем дозе антикоагулантне терапије од стандардних, до интермедијарних или чак терапијских. Међутим, објављени подаци о учесталости и исходу хеморагијских компликација примењених протокола лечења су и даље ограничени.

Приказ болесника У тексту се приказују две болеснице са ковидом 19 и појавом масивног крварења (спонтани ретроперитонеални хематом) као последицом примењене антикоагулантне терапије. Прва, 64-годишња, болесница примљена је у Јединицу интензивног лечења због тешке респираторне инсуфицијенције. Започета је неинвазивна механичка вентилација и терапијска доза антикоагулантне терапије одређена вредностима анти-*Xa* теста. Кумулативна доза надропарина је била 150 *IU/kg* телесне масе по дану. Код друге, 60-годишње, болеснице са билатералном пнеумонијом и умерено тешком клиничком сликом примењене су терапијске дозе антикоагулантне терапије израчунате према телесној тежини. Обе болеснице су пребачене у другу установу и подвргнуте хитној хируршкој интервенцији због значајног крварења. Активно хируршко крварење није откривено, а ретроперитонеални хематоми се сматрају компликацијом примењене терапије. Обе болеснице су отпуштене са лечења у добром општем стању.

Закључак Масивно крварење представља ретку али могућу компликацију антикоагулантне терапије код болесника са ковидом 19. Неуобичајена места спонтаног крварења захтевају индивидуални терапијски приступ болеснику, с обзиром на то да се дијагноза често одлаже због недостатка специфичних симптома. Потребне су даље студије да би се испитале ефикасност и безбедност примене различитих протокола антикоагулантне терапије, посебно виших терапијских доза, код болесника са ковидом 19.

Кључне речи: ковид 19; антикоагулантна терапија; крварење; ретроперитонеум