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Life-threatening Hemorrhagic Conditions in COVID-19 Patients in the Intensive Care Unit: A Case Series

Yoğun Bakım Ünitesinde COVID-19 Hastalarında Hayatı Tehdit Eden Hemorajik Durumlar: Olgu Serisi

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Abstract

The COVID-19 pathology is characterized by thromboinflammatory events at a microvascular level in the lung and other organs. In an assessment of patients with severe COVID-19 pneumonia requiring intensive care, we identified cases in which life-threatening hemorrhage was encountered after the administration of therapeutic/prophylactic-dosage low molecular weight heparin according to guidelines. Among the identified cases, three were male, two female and all patients were administered anticoagulation administrations. All patients with suspected bleeding were identified with severely low hemoglobin levels. Retroperitoneal hematomas were detected in four of the five patients, one of whom was diagnosed based on clinical suspicion, while others were confirmed via imaging. One patient died due to hemorrhage, while the hemorrhages of other patients were controlled through the discontinuation of anticoagulant therapy and appropriate blood product transfusions. While administering anticoagulant therapy for COVID-19 pneumonia in patients followed in the intensive care unit, attention should be paid to the issue of bleeding, and the potential for such rare but life-threatening complications as retroperitoneal hematoma.

Keywords: *COVID-19, retroperitoneal hematoma, anticoagulant therapy, bleeding.*

Öz

COVID-19 patolojisi; akciğer ve diğer organlarda mikrovasküler seviyede tromboinflamatuvar olaylar ile karakterizedir. Yoğun bakım gerektiren ağır COVID-19 pnömonili hastalara kılavuzlara göre terapötik/profilaktik dozda düşük moleküler ağırlıklı heparin uygulamasından sonra karşılaşılan hayatı tehdit eden kanama olgularını derledik. Olguların üçü erkek, ikisi kadındı ve hepsine antikoagülasyon uygulandı. Kanama şüphenilen hastaların hepsinde ciddi hemoglobin düşüklüğü mevcuttu. Biri klinik şüphe ile tanı konulan, diğerleri görüntüleme yöntemleri ile kesinleşen 5 hastanın dördünde retroperitoneal, birinde iliopsoas kası içinde hematom tespit edildi. Bir hasta hemoraji nedeniyle kaybedilirken, diğer hastaların hemorajileri antikoagülan tedavinin sonlandırılması, uygun kan ürünü transfüzyonları ile kontrol altına alındı. Yoğun bakım ünitesinde takip edilen COVID-19 pnömonili olgularda antikoagülan tedavi verilirken kanama açısından dikkatli olunmalı ve hastalar vital bulgular ve laboratuvar bulguları ile sık monitorize edilmeli, retroperitoneal hematom gibi nadir ancak hayatı tehdit edebilecek komplikasyonlar akılda tutulmalıdır.

Anahtar Kelimeler: *COVID-19, retroperitoneal kanama, antikoagulan tedavi, kanama.*

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Coronavirus disease-2019 (COVID-19), caused by the SARS-CoV-2 virus, is a public health problem that emerged in the final days of 2019 and was ultimately declared a pandemic (1). The disease may present with different clinical characteristics, ranging from asymptomatic to severe acute respiratory distress syndrome (ARDS). In addition to respiratory problems, extrapulmonary manifestations and complications have also been reported (2). The available data suggest that the pathophysiology of the disease is characterized by thromboinflammatory events at a microvascular level in the lung, central nervous system, heart, kidney, liver and stomach, among other organs (3). COVID-19-associated coagulopathy leads to a prothrombotic state, with a venous thromboembolism prevalence of up to 69% in critically ill patients, irrespective of the use of pharmacological thromboprophylaxis, and reported arterial thrombosis (4). The virus binds to the ACE-2 receptors on the endothelial surface and activates the infection-related coagulopathy cascade (3). These thromboinflammatory reactions can present as venous thromboembolism, deep vein thrombosis, acute coronary syndrome, stroke, sepsis-induced coagulopathy and disseminated intravascular coagulation, while in laboratory findings, these developments can present with increased levels of fibrinogen, D-dimer and interleukin (IL)-6 levels, and decreased antithrombin and lymphocyte levels. In the light of this information, and based on the recommendations of the World Health Organization (WHO), prophylactic or therapeutic anticoagulators should be administered to all patients hospitalized with COVID-19, although there is still a lack of consensus on the dose or duration of such therapies, which can lead to such problems as life-threatening hemorrhages. In cases where such complications develop, therefore, the characteristics of the patient and the treatment approach should be investigated thoroughly. In an assessment of patients with severe COVID-19 pneumonia requiring intensive care, we identified cases in which life-threatening hemorrhage was encountered after the administration of therapeutic/prophylactic-dosage low molecular-weight heparin according to the guidelines of WHO and the Turkish Ministry of Health during the period in which patients were admitted to our intensive care unit.

Diagnostic and Therapeutic Approach: Based on the WHO and Turkish Ministry of Health guidelines, all of the below cases can be considered severe COVID. All patients had a respiratory rate of >30 breaths per minute; oxygen saturation (SpO_2) levels were below 90% in room air, and bilateral diffuse pneumonia findings were identified on chest X-ray and tomography. All patients were treated in the intensive care unit due to a P/F ratio below 300 and SpO_2 below 90%, despite 5lt/min of oxygen. The patients were started on low molecular weight heparin (LMWH) in accordance with their body weight, and depending on the severity of their COVID infection and D-Dimer levels. Of the 261 patients, 216 were administered prophylactic doses of LMWH and hospitalized in the intensive care unit, while a therapeutic dose of LMWH was administered to the other 45 cases.

CASE

Case 1: A 50-year-old male patient with known asthma and hypertension (HT) being treated in the chest diseases ward for COVID-19 pneumonia was intubated after developing respiratory failure, and was admitted to the intensive care unit. He was not on any medications other than inhaled corticosteroid (ICS) and long-acting beta2-agonist (LABA) treatments. On physical examination, his heart rate (HR) was regular at 101/minute, blood pressure (BP) was 126/50 mmHg, respiratory rate (RR) was 32/minute and SpO_2 was 92% (with 60% FiO_2), while a respiratory system examination revealed bilateral crepitant rales and expiratory rhonchi in all regions. The patient's partial oxygen pressure/fraction of inspired oxygen (P/F) ratio was 78 mmHg. He weighed 55 kg, had a Body Mass Index (BMI) of 21, an Acute Physiology and Chronic Health Evaluation (APACHE II) score of 20, and a Wells score (pulmonary thromboembolism clinical prediction score) of 1.5. Mechanical ventilation support was started in SIMV(PC)/PSV mode with a PEEP (positive end-expiratory pressure) value of 8, inspiratory pressure (PIP) of 25 and RR of 15/min.

The patient was initiated on methylprednisolone (80 mg/day), tocilizumab 800mg/day and subcutaneous enoxaparin (4000 anti-Xa IU, twice daily). The patient was extubated on the 11th day of hospitalization, but reported pain in the lower left lower quadrant, while decreases in hemoglobin (Hb) and hematocrit (Hct) levels were reported on the 13th day of hospitalization. An abdomen computed tomography (CT) was subsequently ordered revealing hematoma development in the left retroperitoneal region and in a small area in the right retroperitoneal region (Figure 1). The patient's anticoagulant treatment was stopped and appropriate blood transfusions were applied, and a decision for follow-up with general surgery and interventional radiology consultations was made. The patient, whose Hb and Hct levels did not decrease during follow-up was discharged to the ward after demonstrating clinical and radiological improvement.

Case 2: A 76-year-old male patient with known HT and coronary artery disease (CAD) (bypass operation 6 years prior) applied to the emergency department with cough and shortness of breath, and was admitted to our intensive care unit after requiring intubation in the emergency clinic due to COVID-19 pneumonia and respiratory fail-

ure. The patient was regularly using acetylsalicylic acid and enalapril. On physical examination, his HR was 111/min, BP was 87/63 mmHg, RR was 42/min and SpO_2 was 93% (with 100% FiO_2), while respiratory sounds were decreased on auscultation. The P/F ratio was 105 mmHg, BMI was 33.06 (with 90 kg), APACHE II score was 19 and Wells score was 1.5.

The patient was initiated on methylprednisolone (250 mg for 3 days, then 40 mg) and subcutaneous enoxaparin (6000 anti-Xa IU, twice daily), and on the 18th day of hospitalization with invasive mechanical ventilation, an abdominal CT was ordered to detect a possible bleeding focus due to an increase in inotrope need and a decrease in Hb values. CT revealed opacity consistent with bleeding to the posterior of the right kidney (Figure 2). The patient's anticoagulant treatment was stopped and the appropriate blood product transfusions were made, but the patient died of septic shock on the 25th day of hospitalization, despite the bleeding being brought under control.

Case 3: A 62-year-old female patient with known chronic obstructive pulmonary disease (COPD), HT, CAD and peptic ulcer was hospitalized in the chest diseases ward with COVID-19 pneumonia, and was admitted to the intensive care unit due to desaturation (SaO_2 with a reservoir mask: 85%) and the development of atrial fibrillation (AF) with rapid ventricular response. She was regularly using metoprolol 50 mg/day, Olmesartan 20 mg/day, acetylsalicylic acid 100 mg/day and quetiapine 25mg/day. A physical examination at the time of admission to the intensive care unit revealed the patient to be conscious, oriented and cooperative, while HR was 120/min (with AF), BP was 130/73 mmHg, RR was 33/min and SpO_2 was 85% (15 L/min O_2 with a reservoir mask). A respiratory system examination revealed crepitant rales bilaterally in all regions on auscultation. Here P/F was 82 mmHg, BMI was 30 (with 70 kg), APACHE II score was 15 and Wells score was 1.5.

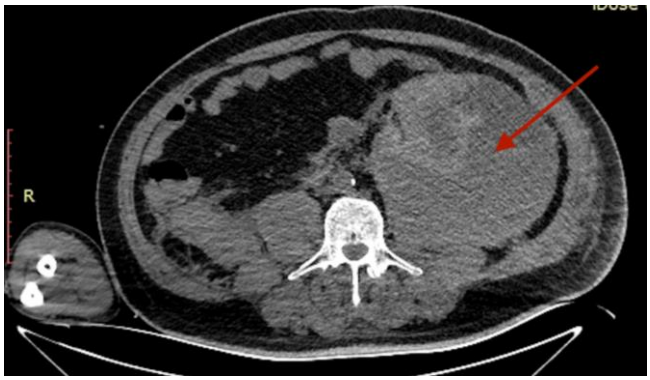

Figure 1: Axial abdomen CT section of Case 1: hematoma in the right and left retroperitoneal regions

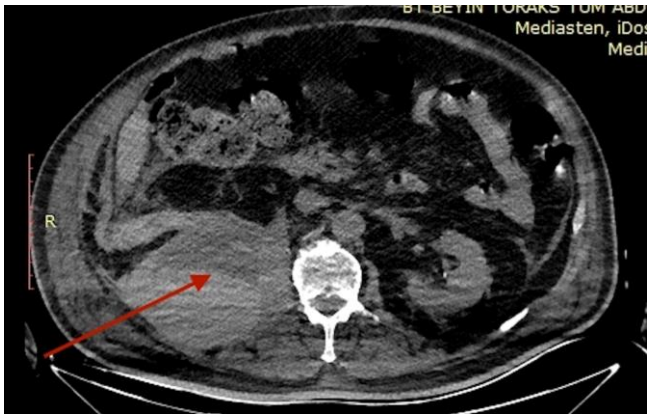

Figure 2: Axial abdomen CT section of Case 2: hematoma in the right retroperitoneal region

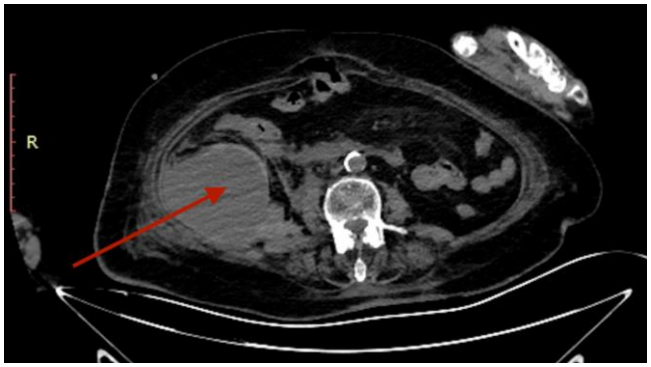

Figure 3: Axial abdomen CT section of Case 3: right retroperitoneal hematoma extending to the right femoral region

Intermittent non-invasive mechanical ventilation (NIMV) and high flow nasal oxygen (HFNO) were applied with a target SpO_2 of 95%, and the patient was started on subcutaneous enoxaparin (6000 anti-Xa IU, twice daily), and methylprednisolone (250 mg for 3 days, then 80 mg), while her other treatments were continued. The patient had atrial fibrillation, and so a treatment dose of anticoagulant was started. On the 5th day of hospitalization, an abdominal CT was ordered due to severely low Hb and Hct values and ecchymosis in the right femoral region, which led to the detection of a right-sided retroperitoneal hemorrhage extending to the femoral region (Figure 3). The patient's anticoagulant and antiaggregant drugs were discontinued and the appropriate blood product transfusion therapy was started. After consultation with the general surgery, interventional radiology and cardiovascular surgery departments, an interventional procedure for the hematoma was deemed unnecessary. On the 13th day of intensive care hospitalization the patient's clinical, radiological and laboratory findings improved and she was transferred to the ward.

Table 1: Laboratory findings on the days when the cases were admitted to the intensive care unit and bleeding was detected

	Case 1		Case 2		Case 3		Case 4		Case 5	
	1st day	11th day	1st day	18th day	1st day	5th day	1st day	16th day	1st day	18th day
BUN	35	74	61	59	76	92	16	80	27	102
Creatinine	0.86	1.53	1.16	0.84	1.13	1.17	1.11	0.49	0.96	1.76
Hct	44.9	20.2	33	22.5	32	23.2	36.6	19.9	43	23,7
Hb	15.2	6.9	11.2	7.5	10.5	7.17	12.3	6.6	14.6	7.7
PLT	211	274	190	101	296	242	413	297	199	146
aPTT	26.5	28.7	30.9	33.5	34	33.7	48.6	34.2	31.7	36.8
INR	0.9	1.5	1.1	1.2	1.2	1.1	0.47	1.2	1	2.3
D-Dimer	1.85	-	1.11	2.43	0.67	1.28	1.2	1.4	0.19	1.25
Fibrinogen	571	147	946	415	668	397	364	335	610	-
Ferritin	571	789	905	538	504	209	2000	343	1120	948
LDH	705	241	549	512	301	435	492	334	3.5	900

BUN: *Blood Urea Nitrogen,* **Hct:** *Hematocrit,* **Hb:** *Hemoglobin,* **PLT:** *Platelet,* **aPTT:** *Active Partial Tromboplastin Time,* **INR:** *International Normalized Ratio,* **LDH:** *Lactate dehydrogenase*

Case 4: A 47-year-old female patient who had undergone surgery due to a lacrimal gland adenoid cystic carcinoma 10 years earlier and was receiving immunotherapy, with no history of any other chronic diseases or drug use, suffered an in-home cardiac arrest while being followed up at home for COVID-19, and was ultimately admitted to the intensive care unit after being intubated following approximately 20 minutes of CPR. A physical examination revealed HR of 88/min, BP of 110/60 mmHg, RR of 38/min and SpO_2 of 98% (with 40% FiO_2). P/F was 100 mmHg, the BMI of the patient was 31 (with 75 kg), her APACHE II score was 26 and her Wells score was 1.

The patient was started on dexamethasone (6 mg), and subcutaneous enoxaparin (6000 anti-Xa IU, twice daily). The patient, while receiving IMV via orotracheal intubation (OTE), was identified with severely decreased hemoglobin levels on the 16th day of hospitalization, and so was scheduled for CT. CT imaging revealed a hematoma in the left iliopsoas muscle (Figure 4), and so the anticoagulant treatment was discontinued and a suitable treatment was started. The patient was discharged to the ward on the 22nd day of hospitalization after the hematoma regressed.

Case 5: A 56-year-old male patient with known ischemic heart disease (IHD), HT and diabetes mellitus (DM) was hospitalized in the chest diseases department due to COVID-19 pneumonia, and was subsequently extubated and admitted to the intensive care unit. The patient was being treated with acetylsalicylic acid 100mg/day, carvedilol 6.25 mg/day and oral antidiabetic drugs. On physical examination, his heart rate (HR) was regular at 98/minute, blood pressure (BP) was 110/80 mmHg, respiratory rate (RR) was 45/min and SpO_2 was 88% (with 60% FiO_2), while a respiratory system examination revealed bilateral crepitant rales and expiratory rhonchi in all regions. The patient's P/F was 60 mmHg, BMI was 22 (with 71 kg), APACHE II score was 14 and Wells score was 1.

The patient was followed up with alternating HFNO/NIMV, methylprednisolone (250 mg for 3 days, then 80 mg), subcutaneous enoxaparin (4000 anti-Xa IU, once daily) and acetylsalicylic acid 100 mg/day treatments were initiated, along with tocilizumab 800 mg and stem-cell therapy. On the 15th day of hospitalization, the patient's anticoagulant dosage was switched to a therapeutic dose, and on the 18th day of hospitalization, the patient was found to have severely decreased hemoglobin and hematocrit, and deepened hypotension. Although imaging could not be performed due to the poor general condition of the patient, other bleeding localizations were excluded and so the patient was considered to have retroperitoneal bleeding. As a result the anticoagulant treatment was discontinued and appropriate treatments were started, however, the patient died on the 23rd day of treatment.

Figure 4: Axial abdomen CT section of Case 4: hematoma extending along the left iliopsoas muscle

The laboratory findings of the patients, on the day of admission to the intensive care unit and on the day in which bleeding was detected, are summarized in Table 1.

DISCUSSION

With regard to the association between COVID-19 and thromboembolic events in hospitalized patients, there has been an increase in the use of anticoagulants, in accordance with the produced guidelines. This has led to an increase in serious bleeding events in patients on prophylactic or therapeutic doses of anticoagulants. The risk of bleeding is known to be high in hospitalized patients who use anticoagulants, regardless of COVID-19 (5). Furthermore, the use of anticoagulants together with antiaggregant or antiplatelet agents such as aspirin increases the risk of bleeding even more (6). Although predisposition to bleeding is rare in COVID-19, previous have associated such events with impaired thrombocyte production, coagulation dysfunction and imbalances in antithrombotic prophylaxis (7-9)

Among the cases presented here, following the recommendations of WHO and the Ministry of Health COVID-19 at that time, a therapeutic dose of anticoagulants was given to patients with severe pneumonia, to those requiring intensive care and to those with high D-dimer levels, and the treatment was continued if the patient had previously been treated with antiaggregant or antiplatelet therapies. Only one of our patients (case 5) was started on a prophylactic dose due to a low D-dimer level, and although imaging could not be performed on the 15th day of hospitalization, the therapy was increased to a therapeutic dose due to increased D-dimer levels and a FiO_2 need. In most of the cases reported in the literature, anticoagulant doses were administered at the treatment dose (10–13).

A review of literature reveals a noteworthy finding that patients with bleeding had comorbid diseases. All of our cases had comorbidities, among which HT, DM and IHD were the most common. The acetylsalicylic acid treatments of three patients with IHD were continued. In the early stages of the pandemic, different opinions were voiced regarding acetylsalicylic acid treatment, and its use was left to the discretion of physicians depending on the benefit/risk ratio. Although acetylsalicylic acid was not started as routine in the intensive care unit due to COVID-19, we continued to provide it to patients who used it chronically due to comorbid disease. No acetylsalicylic acid was administered to two of our patients who were not using it previously. It was our opinion that the increase in the incidence of bleeding could be attributed to several factors, including the presence of comorbid diseases, the use of antiaggregants together with anticoagulant therapy, and the use of anticoagulants in therapeutic dosages in all patients. In fact, in our case series, hemorrhagic events occurred in 1.9% of the patients given a therapeutic dose of anticoagulant, and in 0.02% of the patients given a prophylactic dose. In the study carried out by the REMAP-CAP, ACTIV-4a, ATTACC researchers' results disproved the hypothesis that routine therapeutic-dose anticoagulation could be beneficial for patients with COVID-19 (14). At the time of writing, WHO recommends a prophylactic dose of anticoagulant therapy in severe cases of COVID-19 pneumonia indicated for intensive care, except in the presence of other indications.

In conclusion, in cases with COVID-19 pneumonia followed in the intensive care unit, care should be taken for bleeding when anticoagulant therapy is administered, the vital signs and laboratory findings of patients should be monitored frequently, and rare but life-threatening complications such as retroperitoneal hematoma should be kept in mind. Drawing upon information from the available literature and the findings of our own case series, we hope that we can contribute to literature by discouraging clinicians from using high-dose prophylactic anticoagulants when initiating empirical anticoagulants in the absence of specific indications.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - H.K.O., N.B., E.A.O., Ö.D.; Planning and Design - H.K.O., N.B., E.A.O., Ö.D.; Supervision - H.K.O., N.B., E.A.O., Ö.D.; Funding - H.K.O., N.B., E.A.O., Ö.D.; Materials - H.K.O.; Data Collection and/or Processing - H.K.O., N.B.; Analysis and/or Interpretation - H.K.O., N.B.; Literature Review - H.K.O., E.A.O; Writing - H.K.O.; Critical Review - H.K.O.

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