Submitted June 2021; Accepted November 2021

CASE REPORT

The other side of coagulation complications in COVID-19: a case report of two major bleeding events

A. Karels-van den Berg[1]*, J. Rutgers[1]*, H. Endeman[3], E. de Jongh[1,2], M.J.H.A. Kruip[4]
Departments of [1]Internal Medicine, and [2]Haematology, Albert Schweitzer Hospital, Dordrecht, the Netherlands
[3]Intensive Care Unit and [4]Department of Haematology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands

* *The first two authors contributed equally to this work*

Correspondence
J. Rutgers - jojrutgers@hotmail.com

Keywords - **anticoagulation, bleeding, COVID-19, inflammation, thrombosis**

Abstract

Coronavirus disease 2019 (COVID-19) is still an ongoing pandemic and has already resulted in millions of deaths worldwide. Since it is frequently associated with thrombotic complications, most hospitalised patients receive some form of anticoagulant therapy. Lately, bleeding events in patients with COVID-19 have also been increasingly reported. It is not yet clear whether these are also part of the spectrum of coagulation dysfunction in COVID-19. We report two cases of patients with COVID-19 with a large spontaneous haemorrhage during therapeutic anticoagulant therapy, after a long-term stay in the ICU. We propose several hypotheses for the occurrence of bleeding in COVID-19. Physicians should be aware of this risk, especially when patients are being treated with anticoagulants, because changes in the patient's condition during the course of the disease could lead to a relative overdose. We advise regular reassessment of anticoagulation dosage in patients with COVID-19.

Introduction

In December 2019, a new coronavirus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged in the region of Wuhan, in China. Since then, the virus has been spreading across the whole world, resulting in an ongoing pandemic. The disease caused by this novel virus is known as Coronavirus Disease 2019 (COVID-19), which mostly manifests with symptoms of fever, cough and/or dyspnoea.[1]

Studies have described coagulation abnormalities in patients with COVID-19, which seem to be related to the severity of the disease.[2,3] The occurrence of thromboembolism is frequently reported in hospitalised COVID-19 patients. The incidence appears to be higher in severely ill patients, in particular those who are admitted to the ICU. Cumulative incidence rates of up to 31% are documented in ICU patients.[2-4] Therefore, both prophylactic and therapeutic anticoagulants are often prescribed in COVID-19 patients.[5]

Much less has been published about the occurrence of bleeding in COVID-19 patients, although studies on this subject have increased lately.[2,6-12] It is not yet clear whether this complication is also part of the spectrum of coagulation dysfunction in COVID-19.

We report two cases of patients with COVID-19 with a large spontaneous haemorrhage during therapeutic anticoagulant therapy, after a long-term stay in the ICU. We propose several hypotheses for the occurrence of bleeding events in COVID-19 patients.

Cases

Patient A, a 73-year-old man with a history of atrial fibrillation for which he was taking rivaroxaban, was admitted to the hospital with symptoms of general malaise for more than a week and dyspnoea. On admission, the patient was moderately ill. Apart from mild hypoxaemia, for which he required oxygen therapy, no other significant abnormalities were reported on physical examination. Computed tomography angiography (CTA) of the chest showed widespread bilateral ground glass opacities and dorsobasal consolidations, suspect for COVID-19 (CO-RADS 5, classified as 'very high suspicion' and a severity score of 15 out of 25).[13,14] Shortly after, this diagnosis was confirmed by reverse transcription polymerase chain reaction (RT-PCR).

Within one day after admission, the patient was transferred to the ICU for intubation because of respiratory insufficiency. Rivaroxaban was then replaced by low-molecular-weight heparin (LMWH) in a therapeutic dose of 10,000 international units (IU) twice daily subcutaneously.

Several CTAs were performed during his stay in the ICU, which showed signs of extensive consolidations and fibrosis, but no pulmonary emboli. Finally, the patient's condition slowly improved and after 38 days in the ICU he was discharged to the COVID-19 step down ward.

Two days later, the patient complained of right-sided chest pain. On physical examination, a painful swelling with a diameter of about 15 cm on the right lateral side of the chest just below the axilla was found. There were no visible signs of inflammation or bleeding. Laboratory tests showed a decrease in haemoglobin, as compared with two days before (*table 1*).

Suddenly, the patient's condition deteriorated, showing the clinical presentation of hypovolaemic shock. Fluid resuscitation was immediately given, followed by blood products as severe haemorrhage was suspected. Emergency CTA of the chest showed a large haematoma in the right latissimus dorsi muscle with signs of active bleeding originating from the thoracodorsal artery (*figure 1*). Coil embolisation was successfully performed and the patient was then transferred to the ICU for further stabilisation.

In the following days, the patient needed several blood transfusions because of declining haemoglobin levels. Ongoing or new blood loss was excluded by repeated CTAs. Subsequently, he developed severe pneumonia and delirium. Despite administration of antibiotics and oxygen therapy, the patient's condition deteriorated further and eventually he died one and a half months after initial admission to the hospital.

Patient B, a 63-year-old man with a history of diabetes mellitus type 2, hypertension and chronic mild kidney dysfunction, presented to the emergency department with a ten-day history of general malaise. On physical examination, the patient was found to have a sinus tachycardia, hypoxaemia and severe tachypnoea. The chest radiograph showed bilateral consolidations, suspect for COVID-19. Ceftriaxone and oxygen were administered.

Within 24 hours after admission, the patient had to be transferred to the ICU for intubation due to respiratory insufficiency. CTA of the chest demonstrated widespread abnormalities, compatible with COVID-19 (CO-RADS 5 and a severity score of 19 out of 25) and no signs of pulmonary embolism.[13,14] SARS-CoV-2 RNA was detected in a nasopharyngeal swab specimen by RT-PCR.

Because of hypercoagulability in COVID-19, prophylactic LMWH 5,000 IU twice daily was started according to the local protocol at that time. The patient was discharged to the COVID-19 step down ward after two weeks, but had to be readmitted to the ICU two days later because of respiratory insufficiency. CTA was suspicious for segmental and subsegmental pulmonary emboli, for which the prophylactic LMWH dosage was increased to a therapeutic dose of 10,000 IU twice daily subcutaneously.

After a four-day stay in the ICU, the patient returned to the step down ward again. Unfortunately, repeated respiratory insufficiency led to readmission to the ICU on the same day. CTA demonstrated extensive consolidations and fibrosis. Bronchoalveolar lavage showed a herpes simplex virus type 1. Treatment with acyclovir intravenously for 14 days was then started. In total, the patient stayed in the ICU for approximately six weeks; for about five of these six weeks he was mechanically ventilated.

Two days after his third return from the ICU, the patient complained of left-sided chest pain. Physical examination revealed a local swelling, extending to the back. Laboratory studies showed a decrease in haemoglobin (*table 1*). Apart from a sinus tachycardia, the patient was otherwise haemodynamically stable. The LMWH was discontinued and the haemoglobin level was monitored and remained stable during the following hours. The next day, a CTA was conducted that demonstrated a

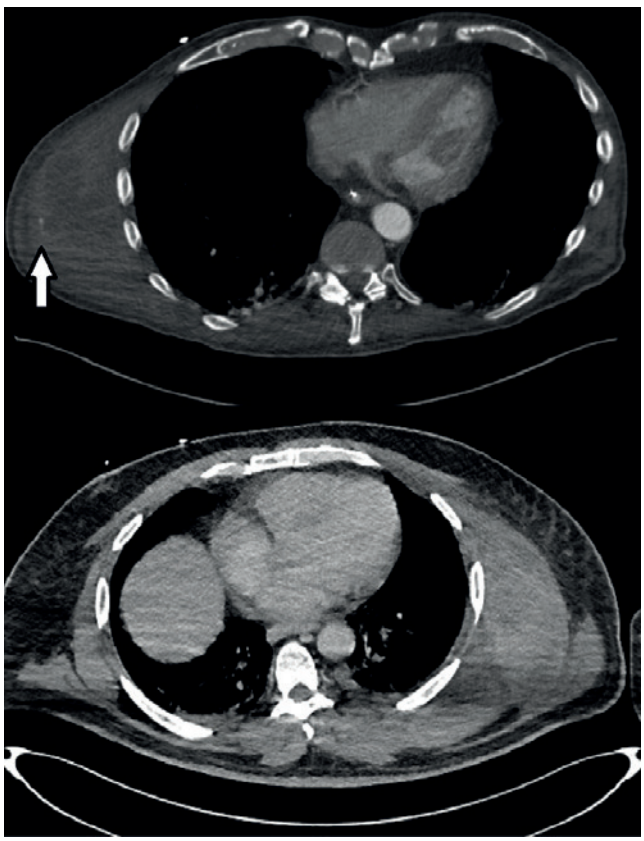

Figure 1. CTA images of patient A and B

Top: axial thoracic image of patient A, arterial phase. Large haematoma in the soft tissues on the right lateral side of the thorax with signs of active bleeding: active contrast extravasation from a side branch of the right subclavian artery (see arrow), probably the thoracodorsal artery, which mainly perfuses the latissimus dorsi muscle.

Bottom: axial thoracic image of patient B, late phase. Large haematoma alongside the left dorsolateral thoracic wall. No signs of active bleeding.

large haematoma along the dorsolateral thoracic wall with no evidence of active bleeding (*figure 1*). The patient received a blood transfusion. As there were no signs of rebleeding, therapeutic anticoagulant therapy was restarted two days later. Peak anti-Xa activity was measured four hours after the first dose and was just below the therapeutic level. No new bleeding complications occurred. In the following days, the patient showed clinical improvement and he could be discharged to a rehabilitation centre two weeks later.

Both patient A and B had tested negative for SARS-CoV-2 three weeks after they experienced their first symptoms. There had been no trauma in either case before the bleeding occurred. They both received chloroquine for five days, according to the former standard treatment for COVID-19 in our hospital, and selective digestive decontamination based on cultures during their stay in the ICU. Dexamethasone was not administered, since this was not standard care at that time. Neither patient was receiving relevant co-medication such as other anticoagulants or non-steroidal anti-inflammatory drugs.

Discussion

In January 2020, the COVID-19 outbreak was declared a Health Emergency of International Concern by the World Health Organisation (WHO).[15] Despite all kinds of measures that have been taken and increasing vaccination rates across the world, new cases and deaths are still added worldwide every day, making SARS-CoV-2 a persistent threat to international public health.

Table 1. Laboratory values of patient A and B

	Unit	Reference values	At admission*1	Days before bleeding*2	During bleeding	Day after bleeding *3
Patient A						
Hemoglobin	mmol/L	8.5 - 11.0	9.0	6.4	5.3	7.5
Thrombocytes	10e9/L	150 - 400	300	243	312	229
aPTT	sec	- 32	30	29		25
PT	sec	8 - 11	13	13		12
Fibrinogen	g/L	2.0 - 4.0				3.9
INR						1.1
Leucocytes	10e9/L	4.3 - 10.0	8.5	9.4	22.0	29.0
CRP	mg/L	0 - 10	144	5	7	12
Procalcitonin	ug/L	- 0.10	0.15	0.06		
eGFR	mL/min	90 -	85	> 90	> 90	> 90
Creatinine	umol/L	59 - 104	78	46	37	43
Urea	mmol/L	2.5 - 6.4	5.0	8.3		9.4
Patient B						
Hemoglobin	mmol/L	8.5 - 11.0	10.6	6.1	4.8	5.4
Thrombocytes	10e9/L	150 - 400	275	463	415	354
aPTT	sec	- 32	27	31		33
PT	sec	8 - 11	11	12		
Fibrinogen	g/L	2.0 - 4.0				5.0
INR						1.2
Leucocytes	10e9/L	4.3 - 10.0	8.8	10.6	20.4	16.9
CRP	mg/L	0 - 10	179	27		173
Procalcitonin	ug/L	- 0.10	0.86			
eGFR	mL/min	90 -	48	78		45
Creatinine	umol/L	59 - 104	135	90		142
Urea	mmol/L	2.5 - 6.4	14.0	6.7		12.4

aPTT: Activated partial thromboplastin time; PT: Prothrombin time; CRP: C-reactive protein; eGFR: Estimated glomerular filtration rate
*1: All values are from day of admission, except for procalcitonin, aPTT and PT (1 day after admission).
*2: All values are from two days before bleeding, except for aPTT and PT (4 days and 3 days before bleeding in patient A and B, respectively).
*3: Coagulation parameters were measured after transfusion (of four erythrocyte concentrates, two units of fresh frozen plasma (FFP) and administration of 750 IU prothrombin complex and 25 mg protamine in patient A and two erythrocyte concentrates in patient B).

Because COVID-19 is a relatively new disease, knowledge about its pathophysiology, associated symptoms and treatment is still developing. It has become clear that thromboembolism is a frequently occurring complication.[2-4]
Prophylactic treatment with anticoagulants (LMWH or unfractionated heparin) in all hospitalised patients with COVID-19 and therapeutic anticoagulant treatment in all patients with established thromboembolism, is officially recommended.[5] However, there is a high variability in the dosage of thromboprophylaxis used. COVID-19 patients without confirmed thromboembolism, but with a high risk of developing thrombosis, are sometimes treated with anticoagulants in low, intermediate or therapeutic doses. This decision is not always based on guidelines and practice varies among different hospitals and countries.[16]

On the other hand, the occurrence of bleeding complications in patients with COVID-19 has also been reported, ranging from mild to severe with haemodynamic instability. Reported incidence rates vary, but significant or major bleeding events are described in up to 21% of COVID-19 patients admitted to the ICU. Most of the described bleeding cases received a therapeutic dose of anticoagulants, including some patients without confirmed thromboembolism.[2,6-12] Thromboprophylaxis as well as therapeutic treatment with LMWH are known to increase the risk of bleeding. Nevertheless, the rate of major bleeding in COVID-19 patients is higher than would be expected based on the administration of prophylactic or therapeutic LMWH alone.[17,18]

Several other hypotheses for the manifestation of these spontaneous haemorrhages in COVID-19 have been suggested previously.
Firstly, mechanical causes such as increased intrathoracic or intra-abdominal pressure due to cough or ventilation techniques could lead to rupture of blood vessels. Only rare cases of arterial rupture after severe cough have been documented.[19]
Secondly, COVID-19 patients could have an increased bleeding tendency due to coagulation abnormalities, for example because of thrombocytopenia, disseminated intravascular coagulation (DIC) or vitamin K deficiency.[2,20] Both our patients had normal platelet counts and they did not meet the criteria for overt DIC.[21] Since their admission to the ICU, they both received tube feeding (Protein Plus MF), containing vitamin K.
Thirdly, critical illness in general is associated with an elevated bleeding risk.[2,22] In our patients the bleeding events manifested seven and almost eight weeks after they developed their first symptoms of COVID-19, respectively. Both patients had already tested negative for COVID-19 by RT-PCR a few weeks before the bleeding occurred.
Therefore, the above suggested hypotheses do not offer a plausible explanation for the occurrence of major bleeding in our cases, neither do they sufficiently explain the relatively high number of bleeding events in COVID-19 patients in general. Up to now, there is no indication that the SARS-CoV-2 virus itself has intrinsic procoagulant or anticoagulant properties, as do viral haemorrhagic fevers.

Both patients had an absolute indication for anticoagulant therapy. It is remarkable that in our cases the bleeding events occurred relatively late. However, changing patient characteristics during the course of the disease - such as weight loss, deteriorated renal function and reduction of hyperinflammation - could have led to relative overdosing.
During the period of mechanical ventilation in the ICU, patients often lose a significant amount of weight. Although both our patients had lost about 5 to 10 kg, they still received an adequate anticoagulation dosage based on their weight.
LMWH is partially cleared by the kidneys and COVID-19 can be accompanied with renal failure.[1] Whereas the creatinine levels in our patients were comparable or lower than at the moment when treatment with LMWH was started, estimated glomerular filtration (eGFR) based on creatinine levels could have been overestimated because of substantial muscle decay in both patients.
The hypercoagulable state in COVID-19 is thought to be caused by endothelial inflammation and microvascular damage by the virus, leading to increased vascular permeability and subsequently an increased activity of adhesion cells and cytokines.[23] Coagulation profiles of critically ill COVID-19 patients are characterised by elevated fibrinogen, D-dimer, factor VIII and von Willebrand factor concentrations, consistent with a state of hypercoagulability.[24]
Possibly, improvement in the inflammatory state of our patients led to a diminished circulation of prothrombotic cytokines and a reduction in the upregulation of procoagulant factors such as factor VIII. As Godier et al.[8] have already suggested, this would result in a decrease in 'heparin resistance' and consequently a relative overdose of anticoagulants. As the measured peak anti-Xa activity in patient B was based on only one assessment after the first dose of anticoagulants following a period of discontinuation, this result is unfortunately not indicative of the dosage of anticoagulants when the bleeding occurred. If, for example, accumulation of anticoagulants due to a decreased renal function had led to overdosage at the time of bleeding, this would not have been detectable in this single measurement two days later.[25]

In conclusion, COVID-19 is frequently complicated by thrombotic events, but bleeding manifestations are also increasingly reported. We hypothesise that they are caused by the frequent use of anticoagulants, which can sometimes be relatively overdosed. This could occur due to changes in the patient's condition during the course of the disease, such as body weight, renal clearance and hyperinflammatory state.

Physicians should be aware of the possible elevated bleeding tendency in patients with COVID-19, especially when they are being treated with anticoagulants. Dosage of anticoagulants should be reassessed regularly. We propose to measure anti-Xa activity at least several days after the start of prophylactic or therapeutic anticoagulants, and then depending on the course and severity of disease. For instance, when renal function declines or when patients are clinically improving and their state of hyperinflammation and hypercoagulability decreases. In the ICU, more frequent measurements are recommended than on a COVID-19 ward.

Acknowledgement

We would like to thank P.V.M. Linsen (Department of Radiology, Albert Schweitzer Hospital Dordrecht) for providing the CTA images and accompanying anatomical descriptions.

Disclosures

Informed consent for publication of this case report (and the accompanying images) was obtained from the patient's next of kin (case A) and the patient (case B).

All authors declare no conflict of interest. No funding or financial support was received.

References

1 Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis. 2020:101623.
2 Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood. 2020;136:489-500.
3 Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18:844-7.
4 Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:145-7.
5 Spyropoulos AC, Levy JH, Ageno W, et al. Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020;18:1859-65.
6 Palumbo D, Guazzarotti G, De Cobelli F. Spontaneous Major Hemorrhage in COVID-19 Patients: Another Brick in the Wall of SARS-CoV-2–Associated Coagulation Disorders? J Vasc Interv Radiol. 2020;31:1494-6.
7 Fraissé M, Logre E, Pajot O, Mentec H, Plantefève G, Contou D. Thrombotic and hemorrhagic events in critically ill COVID-19 patients: a French monocenter retrospective study. Crit Care. 2020;24:275.
8 Godier A, Clausse D, Meslin S, et al. Major bleeding complications in critically ill patients with COVID-19 pneumonia. J Thromb Thrombolysis. 2021; doi: 10.1007/s11239-021-02403-9
9 Nadkarni GN, Lala A, Bagiella E, et al. Anticoagulation, Bleeding, Mortality, and Pathology in Hospitalized Patients With COVID-19. J Am Coll Cardiol. 2020;76:1815-26.
10 Musoke N, Lo KB, Albano J, et al. Anticoagulation and bleeding risk in patients with COVID-19. Thromb Res. 2020;196:227-30.
11 Daughety MM, Morgan A, Frost E, et al. COVID-19 associated coagulopathy: Thrombosis, hemorrhage and mortality rates with an escalated-dose thromboprophylaxis strategy. Thromb Res. 2020;196:483-5.
12 Kessler C, Stricker H, Demundo D, et al. Bleeding prevalence in COVID-19 patients receiving intensive antithrombotic prophylaxis. J Thromb Thrombolysis. 2020;50:833-6.
13 Prokop M, van Everdingen W, van Rees Vellinga T, et al. CO-RADS: A Categorical CT Assessment Scheme for Patients Suspected of Having COVID-19-Definition and Evaluation. Radiology. 2020;296:E97-104.
14 Francone M, Iafrate F, Masci GM, et al. Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis. Eur Radiol. 2020;30:6808-17.
15 Coronavirus Disease (COVID-19) Situation Reports [Internet]. [cited 2021 May 19]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
16 Rosovsky RP, Sanfilippo KM, Wang TF, et al. Anticoagulation practice patterns in COVID-19: A global survey. Res Pract Thromb Haemost. 2020;4:969-83.
17 Lloyd NS, Douketis JD, Moinuddin I, Lim W, Crowther MA. Anticoagulant prophylaxis to prevent asymptomatic deep vein thrombosis in hospitalized medical patients: a systematic review and meta-analysis. J Thromb Haemost. 2008;6:405-14.
18 Rein N, Biedermann JS, Meer FJM, et al. Major bleeding risks of different low-molecular-weight heparin agents: a cohort study in 12 934 patients treated for acute venous thrombosis. J Thromb Haemost. 2017;15:1386-91.
19 Conti CB, Henchi S, Coppeta GP, Testa S, Grassia R. Bleeding in COVID-19 severe pneumonia: The other side of abnormal coagulation pattern? Eur J Intern Med. 2020;77:147-9.
20 Dahlberg S, Schurgers L, Schött U, Kander T. Vitamin K deficiency in critical ill patients; a prospective observational study. J Crit Care. 2019;49:105-9.
21 Taylor FB, Toh CH, Hoots WK, Wada H, Levi M, Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost. 2001;86:1327-30.
22 Grimnes G, Isaksen T, Tichelaar YIGV, Brox J, Brækkan SK, Hansen J-B. C-reactive protein and risk of venous thromboembolism: results from a population-based case-crossover study. Haematologica. 2018;103:1245-50.
23 Khandait H, Gandotra G, Sachdeva S, et al. COVID-19 and Hematology-What Do We Know So Far? SN Compr Clin Med. 2020; Oct;1-6.
24 Panigada M, Bottino N, Tagliabue P, et al. Hypercoagulability of COVID-19 patients in intensive care unit: A report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemost. 2020;18:1738-42.
25 Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(Suppl 2):e24S-e43S.