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Thromboelastometry early identifies thrombotic complications related to COVID-19: A case report

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Abstract

COVID-19 is a contagious infectious disease, which quickly spreads worldwide, whose clinical presentation includes from mild flu-like symptoms to pneumonia and severe acute respiratory syndrome. The severe presentation of the disease can affect different organs and systems. Coagulopathy has been associated with a worse clinical outcome, with manifestations such as pulmonary embolism and systemic arterial thrombosis. Thromboelastometry has been used to identify hypercoagulability in early stages of disease. We report the case of a 59-year-old woman with COVID-19 infection complicated by pulmonary embolism and acute arterial thrombosis associated with critical lower limb ischemia requiring amputation. This report showed a case of thrombotic complication in patient with infection caused by novel coronavirus 2019 whose thromboelastometry allowed the early identification of hypercoagulability pattern. This is a single case report and the use of thromboelastometry should be further evaluated in large prospective cohort studies.

Keywords

Thromboelastometry, hypercoagulability, thrombosis, coronavirus, case report

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Background

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), whose wide clinical presentation can vary from mild flu-like symptoms to pneumonia and severe acute respiratory syndrome. The severe presentation of the disease can affect several organs, leading to neurological, cardiac, renal, and coagulation system complications. It is a viral sepsis whose host inflammatory response can be highly intense, associated with systemic thrombotic manifestations.[1–3] Viscoelastic tests (VETs) have been done to assess hypercoagulability in patients with severe COVID-19.[4–6] We present a case of COVID-19 infection complicated by pulmonary embolism (PE) and acute arterial thrombosis in lower limb, whose thromboelastometry test early identified the pattern of hypercoagulability.

Case presentation

A 59-year-old woman with a history of hypertension and diabetes was admitted to the hospital with fever, cough, nasal obstruction, and diarrhea, started 5 days before admission. She denied dyspnea or chest pain. Physical examination revealed axillary temperature 38.5°C, blood pressure 170/102 mm Hg, respiratory rate 20 breaths per minute, and oxygen saturation 93%. She was breathing ambient air. Laboratory tests showed leukocytes 9260 per microliter, D-dimer 2404 ng/mL, and fibrinogen 954 mg/dL. Nucleic acid test of a nasopharyngeal swab was positive for SARS-CoV-2. Computed tomography (CT) of the chest showed ground-glass opacities in both lungs, predominantly peripheral, affecting just over 50% of the pulmonary parenchyma. Ceftriaxone, azithromycin, oseltamivir, prophylactic low molecular weight heparin, and supplemental oxygen through nasal cannula at a rate 2 L/m were started. Rotation

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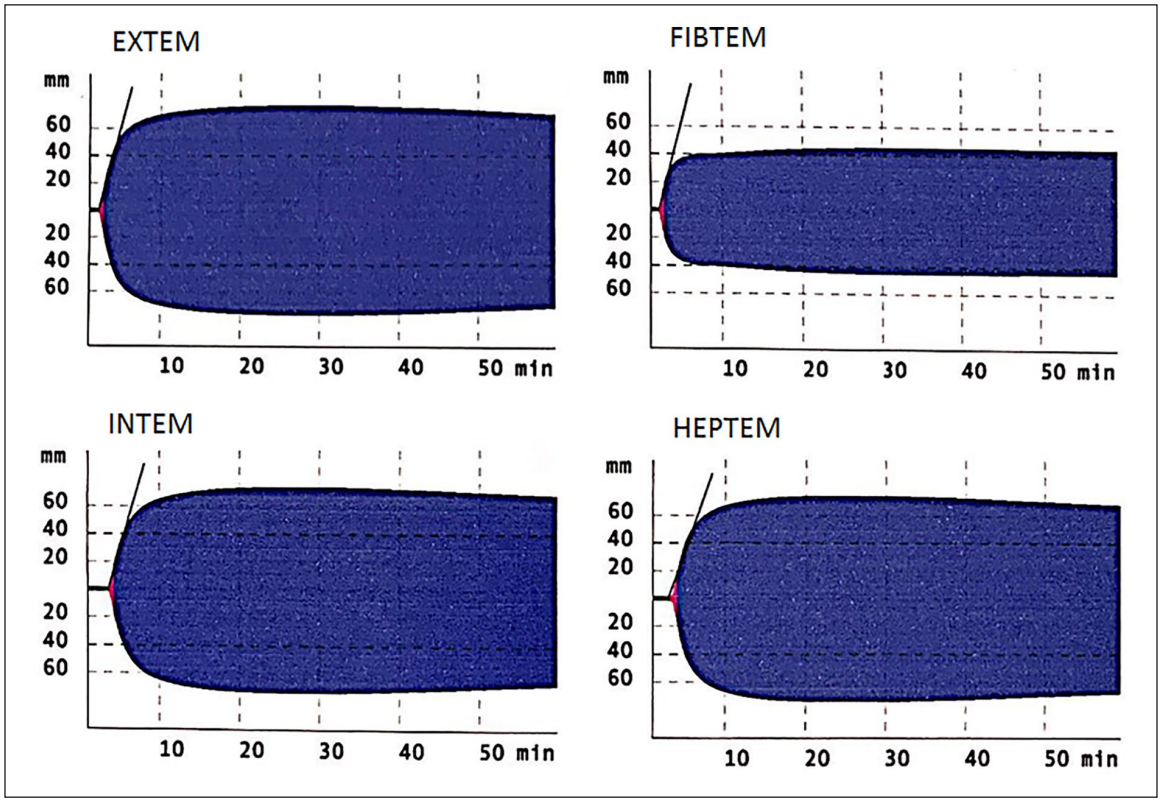

Figure 1. Thromboelastometry showing hypercoagulable state.

Table 1. Thromboelastometry parameters.

	EXTEM		FIBTEM		INTEM		HEPTEM	
	Value	Normal range	Value	Normal range	Value	Normal range	Value	Normal range
CT (s)	76	38–79	69	38–62	163	100–240	127	–
CFT (s)	39	34–159	40	–	43	30–110	63	–
Alpha angle	82	63–83	82	–	81	70–83	79	–
A10 (mm)	73	43–65	42	7–23	70	44–66	71	–
A20 (mm)	77	50–71	45	8–24	74	50–71	74	–
MCF (mm)	77	50–72	46	9–25	74	50–72	74	–
ML (%)	8	0–15	2	–	9	0–15	8	–

ROTEM: rotation thromboelastometry; EXTEM: extrinsically activated (tissue factor) thromboelastometric assay; INTEM: intrinsically activated thromboelastometric assay; FIBTEM: extrinsically activated thromboelastometric assay with the addition of cytochalasin to eliminate platelet contribution to clot firmness; HEPTEM: intrinsically activated thromboelastometric assay with the addition of heparinase; CT: coagulation time; CFT: clot formation time; A10: amplitude of clot firmness 10 min after CT; A20: amplitude of clot firmness 20 min after CT; MCF: maximum clot firmness; ML: maximum lysis during run time.

thromboelastometry (ROTEM) was performed on admission and presented a hypercoagulability pattern (Figure 1 and Table 1). One day after the admission, the patient developed tachypnea, dyspnea at rest, and the oxygen saturation decreased to 88% with oxygen through a nasal cannula at a rate of 5 L per minute. The patient underwent intubation and mechanical ventilation. New laboratory tests revealed fibrinogen 729 mg/dL, interleukin (IL)-6 149 antithrombin III 107%, and a significant increase in D-dimer to 40,130 ng/mL. Pulmonary thromboembolism was suspected and treatment with low molecular weight heparin 1 mg/kg twice daily was started. CT angiography of the chest revealed signs of acute pulmonary thromboembolism, characterized by filling defect in posterior and medial basal arterial subsegments of the right lower lobe. She was extubated after 7 days of intubation. Two days after the extubation, the patient developed pain in the right lower limb and in the right second toe turned blue. There were no palpable pulses throughout the ipsilateral

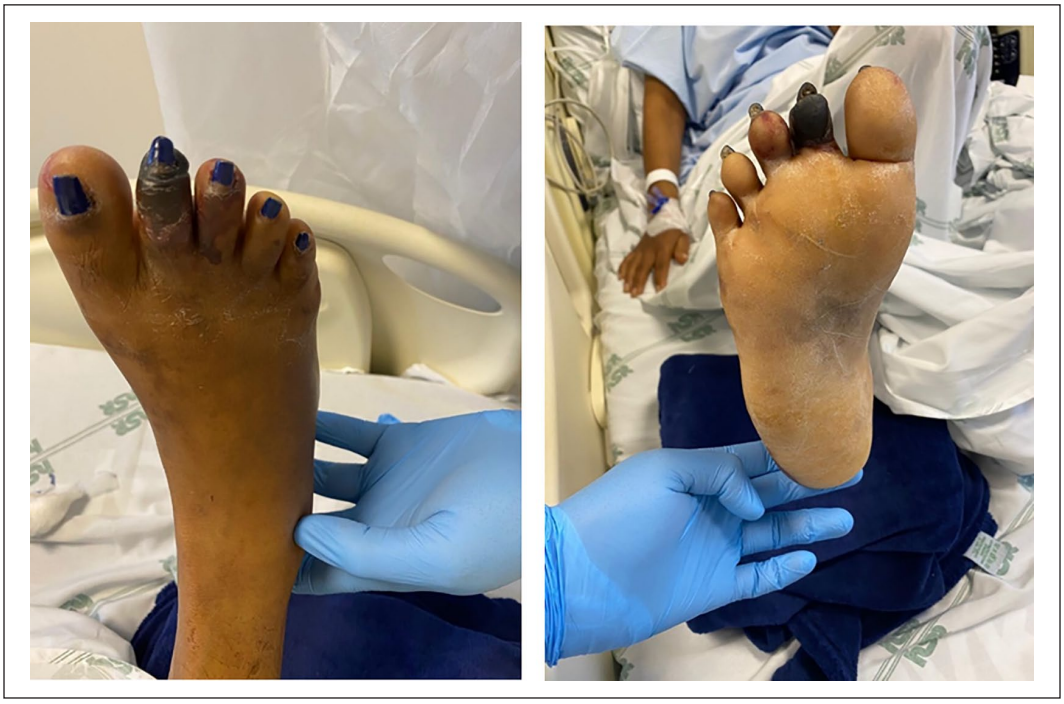

Figure 2. Right second toe arterial ischemia.

lower limb and acute arterial occlusion was suspected (Figure 2). At this moment, the patient had a femoral arterial line in place for blood pressure monitoring, which had been removed. Therapy with anticoagulation was maintained. Venous Doppler of the lower limbs was performed with no evidence of deep venous thrombosis. Transthoracic echocardiogram was unremarkable except for mild tricuspid regurgitation with Right Ventricular Systolic Pressure of 40 mm Hg. She was submitted to arteriography that showed significant stenosis in posterior tibial artery, tibiofibular trunk, and fibular artery, followed by angioplasty of the right lower limb. The anterior and posterior tibial pulses turned palpable, but because of persistent second toe pain, she ultimately underwent amputation of this toe. Two days after the amputation, she was discharged from the hospital taking Apixaban 5 mg twice a day. After 15 days at home, she returned to the vascular surgeon's office with an amputation stump in great condition, denying new complaints and without respiratory symptoms.

This case describes pulmonary thromboembolism and critical limb ischemia in a woman with COVID-19, showing that this disease may predispose to acute arterial thrombosis and the possibility of an early evaluation of coagulation by rotation thromboelastometry in critically ill patients with severe COVID-19.

Discussion

SARS-CoV-2 is a new coronavirus responsible for the current COVID-19 pandemic. Although it is well-documented that COVID-19 is primarily manifested as a respiratory tract infection, data indicate that it should be regarded as a systemic disease involving multiple systems, including cardiovascular, respiratory, gastrointestinal, neurological, hematopoietic, and immune system.[7] Organ dysfunction due to infection has been attributed to a non-adaptive immune response and the complement system.[8] The pathophysiology of severe acute respiratory syndrome related to coronavirus has similarities to that of severe community-acquired pneumonia caused by other viruses or bacteria. The overproduction of early response proinflammatory cytokines (tumor necrosis factor, IL-6, and IL-1β) results in what has been described as a cytokine storm, leading to an increased risk of vascular hyperpermeability, multiorgan failure, and eventually death when high cytokine concentrations are unabated over time.[9] Many patients with severe COVID-19 present coagulation abnormalities that mimic other systemic coagulopathies associated with severe infections, such as disseminated intravascular coagulation (DIC) or thrombotic microangiopathy, but COVID-19 has distinct features.[10] The SARS-CoV-2 virus does not appear to have intrinsic procoagulant effects itself. However, the development of coagulation test abnormalities seen in SARS-CoV-2 infected patients is most likely a result of the profound inflammatory response.[11] A hypercoagulable state appears to be a cornerstone of COVID-19 infection and thrombus formation and deposition in the pulmonary microvasculature can be related to the degree of hypoxemia. It seems to have a deposition of immune complexes inside the vascular walls, and this is supposed to induce a severe inflammatory state and a cytokine

release syndrome whose IL-6 is the key myokine.[12] Roncati et al.[12] have provided a detailed postmortem and biopsy report on the marked increase of naked megakaryocyte nuclei in the bone marrow and lungs from serious COVID-19 patients. Most likely related to high IL-6 serum levels stimulating megakaryocytopoiesis. This phenomenon can explain well the pulmonary abnormal immunothrombosis in these critically ill patients.[13] Deep vein thrombosis (DVT), PE, thrombosis in extracorporeal circuits, and arterial thrombosis have been demonstrated.[1–3] Endeman et al.[14] found the 31% incidence of thrombotic complications in intensive care unit (ICU) patients with COVID-19, of which computed tomography pulmonary angiography (CTPA) and/or ultrasonography confirmed venous thromboembolism (VTE) in 27% and arterial thrombotic events in 3.7%. PE was the most frequent thrombotic complication (81%).

Conventional coagulation tests such as Tp (prothrombin time) and TTpa (activated partial thromboplastin time) are useful tests to monitor the anticoagulant response such as vitamin K antagonists and heparin, respectively. However, these traditional tests fail to identify specific coagulation disorders as hypercoagulability.[15] Plasma D-dimer measurement is commonly used as the first test in patients suspected of DVT. However, some factors limit the usefulness of D-dimer testing among COVID-19-infected patients. Kabrhel et al.[16] conducted a prospective, multicenter, observational study and identified D-dimer has low specificity and many factors such as advanced age, surgery, immobility, and pregnancy can elevate his level. Furthermore, D-dimer reflects a later stage in the hemostatic process and is released when a clot is degraded by the fibrinolytic process.

Faced with the elevated incidence and poor prognosis of VTE and arterial thrombotic complications in COVID-19 patients associated a unavailability of reliably tests that identifies which COVID-19 patients are at the highest risk of developing thromboembolic complications, a correct early diagnosis seems to be crucial for the treatment of coagulopathy with a better clinical outcome. Thromboelastometry or ROTEM is a viscoelastic method that can assess viscoelastic properties of whole blood in contemporary time.[17] The whole process of clot formation includes the initial phase of thrombin generation, maximum clot firmness (MCF), and finally, clot stabilization. This VET was thought as a diagnostic tool in bleeding scenario capable to identify specific disorder of coagulation, such as clotting factor deficiency, thrombocytopenia, hypofibrinogenemia, and heparin effect, guiding hemostatic therapy by goals. ROTEM has been very useful monitoring hemostasis and guiding transfusion requirements.[18] Cochrane review published in 2018 showed that the use of ROTEM intraoperatively and postoperatively in cardiac surgery to guide transfusion of blood products seems to reduce mortality.[19] Traditional conventional tests are poor predictor of bleeding, failing in guide transfusion therapy.

Then, rotational thromboelastometry has also been done to assess hemostasis in COVID-19 patients. Simioni et al. evaluated whole blood thromboelastometry profiles in a group of 22 consecutive patients admitted to the Intensive Care Unit of Padova University Hospital for acute respiratory failure due to COVID-19 and markedly hypercoagulable thromboelastometry profiles were observed in COVID-19 patients, as reflected by shorter clot formation time (CFT) in intrinsically activated thromboelastometric assay (INTEM) and extrinsically activated (tissue factor) thromboelastometric assay (EXTEM) and higher MCF in INTEM, EXTEM, and extrinsically activated thromboelastometric assay with the addition of cytochalasin to eliminate platelet contribution to clot firmness (FIBTEM).[4]

Tripodi et al. evaluated 24 patients admitted at the ICU because of COVID-19 with thromboelastography by the TEG and the parameters were consistent with a state of hypercoagulability.[5] The big doubt is if this hypercoagulability state seen in thromboelastometry is associated with DVT.

A single-center retrospective observational study that evaluated ROTEM parameters confirmed the hypercoagulable state of COVID-19 patients admitted to the ICU. However, it did not support the use of ROTEM® in identifying COVID-19 patients at risk for developing thromboembolic complications.[6]

In this case, the thromboelastometry demonstrated hypercoagulability pattern reflected by short (CFT) in INTEM and EXTEM and high MCF in INTEM, EXTEM, and FIBTEM. This can reflect a hypercoagulability tendency in patients with COVID-19.

Unfortunately, the severity of the thrombotic phenomenon in this patient led to ischemia of the lower limb in need of amputation of the right second toe. Surgical treatment with amputation of this limb was decisive in resolving this case. In retrospectively evaluating this case, we thought about the possibility of using fibrinolytic therapy as an important therapeutic option in the presence of severe systemic acute thrombotic disease.

Conclusion

COVID-19 is a serious infectious disease that leads to an excessive activation of the coagulation system of different forms and intensity and is associated with a worse outcome. This report showed a case of thrombotic complication in patient with infection caused by novel coronavirus 2019 whose thromboelastometry allowed the early identification of hypercoagulability pattern. This is a single case report and the use of thromboelastometry should be further evaluated in large prospective cohort studies.

Author contributions

All the authors listed meet the authorship criteria. R.L.A.S.M., T.C., and F.A.S. wrote the manuscript. F.O.C. helped in obtaining

important pictures. F.O.C. and R.d.H.P. reviewed the manuscript. The authors read and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval and consent to participate

This study is only a retrospective report; therefore, no ethics approval was needed.

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Informed consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Availability of supporting data

The data used in this case report are available from the corresponding author on reasonable request.

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