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...
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

**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.

**Figure 1.** Thromboelastometry showing hypercoagulable state.
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. Organ dysfunction due to infection has been attributed to a non-adaptive immune response and the complement system. 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. 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. 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. 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. Roncati et al. 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 megakaryocytopenosis. This phenomenon can explain well the pulmonary abnormal immunothrombosis in these critically ill patients. Deep vein thrombosis (DVT), PE, thrombosis in extracorporeal circuits, and arterial thrombosis have been demonstrated. Endeman et al. 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. 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. 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 identification of amputation of this limb was decisive in resolving this case. 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.

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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.

References
1. Kashi M, Jacquin A and Dakhil B. Severe arterial thrombosis associated with Covid-19 infection. Thromb Res 2020; 192: 75–77.
2. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020; 191: 9–14.
3. Warrior K, Chung PA, Ahmed N, et al. Acute limb ischemia due to arterial thrombosis associated with coronavirus disease 2019. Crit Care Explor 2020; 2(6): e0140.
4. Spiezia L, Boscolo A, Poletto F, et al. COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. Thromb Haemost 2020; 120(6): 998–1000.
5. 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 haemostasis. J Thromb Haemost 2020; 18(7): 1738–1742.
6. Van Veenendaal N, Scheeren TWL, Meijer K, et al. Rotational thromboelastometry to assess hypercoagulability in COVID-19 patients. Thromb Res 2020; 196: 379–381.
7. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. Am J Hematol 2020; 95(7): 834–847.
8. Fletcher- Sandersjöö A and Bellander BM. Is COVID-19 associated thrombosis caused by overactivation of the complement cascade? A literature review. Thromb Res 2020; 194: 36–41.
9. Jose RJ and Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir Med 2020; 8(6): e46–e47.
10. Levi M, Thachil J, Iba T, et al. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol 2020; 7(6): e438–e440.
11. Connors JM and Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020; 135(23): 2033–2040.
12. Roncati L, Ligabue G, Fabbiani Malagoli C, et al. Type 3 hypersensitivity in COVID-19 vasculitis. Clin Immunol 2020; 217: 108487.
13. Roncati L, Ligabue G, Nasillo V, et al. A proof of evidence supporting abnormal immunothrombosis in severe COVID-19: naked megakaryocyte nuclei increase in the bone marrow and lungs of critically ill patients. Platelets 2020; 31(8): 1085–1089.
14. Klok FA, Kruijk MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020; 191: 145–147.
15. Haas T, Fries D, Tanaka KA, et al. Usefulness of standard plasma coagulation tests in the management of perioperative coagulopathic bleeding: is there any evidence. Br J Anaesth 2015; 114(2): 217–224.
16. Kabrhel C, Mark Courtney D, Camargo CA Jr, et al. Factors associated with positive D-dimer results in patients evaluated for pulmonary embolism. Acad Emerg Med 2010; 17(6): 589–597.
17. Haas T, Gørlinger K, Grassetto A, et al. Thromboelastometry for guiding bleeding management of the critically ill patient: a systematic review of the literature. Minerva Anestesiol 2014; 80(12): 1320–1335.
18. Bonnet A, Gilquin N, Steer N, et al. The use of a thromboelastometry-based algorithm reduces the need for blood product transfusion during orthotopic liver transplantation: a randomised controlled study. Eur J Anaesthesiol 2019; 36(11): 825–833.
19. Wikkelsø A, Wetterslev J, Møller AM, et al. Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding. Cochrane Database Syst Rev 2016(8): CD007871.