Thromboelastometry Early Identifies Thrombotic Complications Related to Covid-19: A Case Report

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Case report

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Abstract

Background: Covid-19 is a contagious infectious disease, which quickly spread worldwide, whose clinical presentation includes from mild symptoms such as flu 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.

Case presentation: 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.

Conclusions: In this case, thromboelastometry allowed the early identification of hypercoagulability pattern. This reported case showed that the early thromboelastometry can be useful to identify hypercoagulable state to guide the anticoagulant therapy and to avoid thrombotic complications.

Background

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a newly discovered SARS-CoV-2, whose wide clinical presentation can vary from mild symptoms like flu 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 or in pulmonary microvasculature. We present our experience of a case of Covid-19 infection complicated by pulmonary embolism 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 comes up to our ICU with fever, cough, nasal obstruction and diarrhea, started five days before admission. She denied dyspnea or chest pain. Physical examination revealed axillary temperature 38.5ºC, blood pressure 170/102 mmHg, 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; 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 and presented a hypercoagulability pattern (Fig. 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 liters per minute. The patient underwent intubation and mechanical ventilation. New laboratory tests revealed fibrinogen 729 mg/dL, interleukin 6 149 antithrombin III 107% and a significant increase in d-dimer to 40130 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 failures in filling in posterior and medial basal arterial subsegments of the right lower lobe. She was extubated after seven days of intubation. Two days after the extubation, the patient developed pain in the right lower limb and the right second toe turned blue. There were no palpable pulses throughout the ipsilateral lower limb and acute arterial occlusion was suspected (Fig. 2). At this moment, the patient had a femoral arterial line in place for blood pressure monitoring, which had been removed. Full therapy with anticoagulation was maintained, and the right lower limb. Venous doppler of the lower limbs was performed with no evidence of deep venous thrombosis was heated. Transthoracic echocardiogram was unremarkable except for mild tricuspid regurgitation with Right Ventricular Systolic Pressure of 40 mmHg. 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 palpably, but because of persistent 2nd toe pain she ultimately underwent amputation. 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.

Table 1
Thromboelastometry parameters

ROTEM	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	-

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, alpha: alpha angle; A10: amplitude of clot firmness 10 minutes after CT; A20: amplitude of clot firmness 20 minutes after CT, MCF: maximum clot firmness; ML: maximum lysis during run time.

Discussion

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new coronavirus (CoV) responsible for the current COVID-19 pandemic. Although it is well documented that COVID-19 is primarily manifested as a respiratory tract infection, emerging data indicate that it should be regarded as a systemic disease involving multiple systems, including cardiovascular, respiratory, gastrointestinal, neurological, hematopoietic and immune system (1). Organ dysfunction due to infection has been attributed to a non-adaptive immune response and the complement system (2). The pathophysiology of severe acute respiratory syndrome related to coronavirus induced ARDS 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 the high cytokine concentrations are unabated over time.(3) 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.(4) 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 are most likely a result of the profound inflammatory response. (5) A hypercoagulable state appears to be a cornerstone of Covid-19 infection. Excessive coagulation activation is a key phenomenon in the pathophysiology of the disease, thrombus formation and deposition in the pulmonary microvasculature can be related to the degree of hypoxemia. Deep vein thrombosis (DVT), pulmonary embolism (PE), thrombosis in extracorporeal circuits and arterial thrombosis have been demonstrated (6). Faced with a complex coagulation disorder, a correct early diagnosis seems to be crucial for the treatment of coagulopathy with a better clinical outcome. 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(7). Thromboelastometry or ROTEM is a point-of care viscoelastic method that can assess viscoelastic properties of whole blood in contemporary time (8). The whole process of clot formation includes the initial phase of thrombin generation, maximum clot firmness and finally, clot stabilization. This viscoelastic test (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. Cochrane review published in 2018 showed that the use ROTEM intraoperatively and postoperatively in cardiac surgery to guide transfusion of blood products seems to reduce mortality, as well as administration of allogeneic blood components(9). Fibrinogen and platelets are both the main determinants of coagulability (8). Fibrinogen concentration can be measured by Clauss Assay and by FIBTEM test (ROTEM). Traditional conventional tests are poor predictor of bleeding, failing in guide transfusion therapy. Fibrinogen is main substrate of clot. Fibrinogen (Factor I) is a glycoprotein that is synthesized in the liver. It is activated to fibrin by thrombin, exposing several polymerization sites that are crosslinked to an insoluble fibrin clot under the involvement of activated factor XIII(10). Activation of the coagulation system and fibrin formation is essential for stopping hemorrhage. The deposition of fibrin is carefully regulated to avoid thrombotic complication by the fibrinolytic system. Plasmin interpose the procoagulant signals, leading to clot dissolution, resulting in the generation of soluble fibrin fragments, such as d-dimers (11).

VETs provide the function of fibrinogen (FIBTEM), as well as the hypercoagulable state in a few minutes at the bedside. Unfortunately, the severity of the thrombotic phenomenon in this patient led to ischemia of the lower limb in need of amputation of this member. 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.

Conclusions

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 reported case showed that the early thromboelastometry can be useful to identify hypercoagulable state to guide the anticoagulant

therapy and to avoid thrombotic complications. Clinical studies are expected to evaluate the role of VETs as a diagnostic tool for coagulopathy in Covid-19, as well as the use of anticoagulants and fibrinolytics in these situations of severe coagulopathy.

Abbreviations

ROTEM- Rotational thromboelastometry

CT- Computed tomography

SARS-CoV-2 - Severe acute respiratory syndrome coronavirus

DIC - disseminated intravascular coagulation (DIC

DVT - Deep vein thrombosis

PE - pulmonary embolism

Tp - prothrombin time

TTpa - activated partial thromboplastin time

VET - viscoelastic test

Declarations

Ethical approval and consent to participate: This study is only a retrospective report; therefore, no ethics approval was needed.

Consent for publication: Patient gave their written consent for publication

Availability of supporting data: The data used in this case report are available from the corresponding author on reasonable request

Competing interests: All the authors declare they have no competing interests.

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authors read and approved the final manuscript.

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Figures

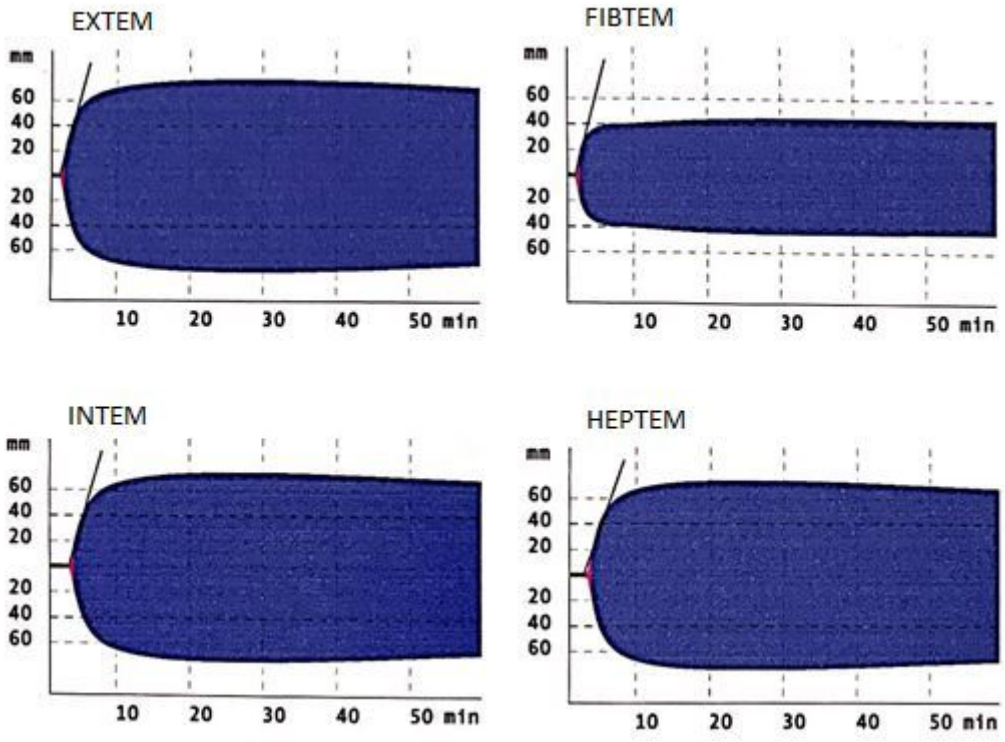

Figure 1

Thromboelastometry showing hypercoagulable state

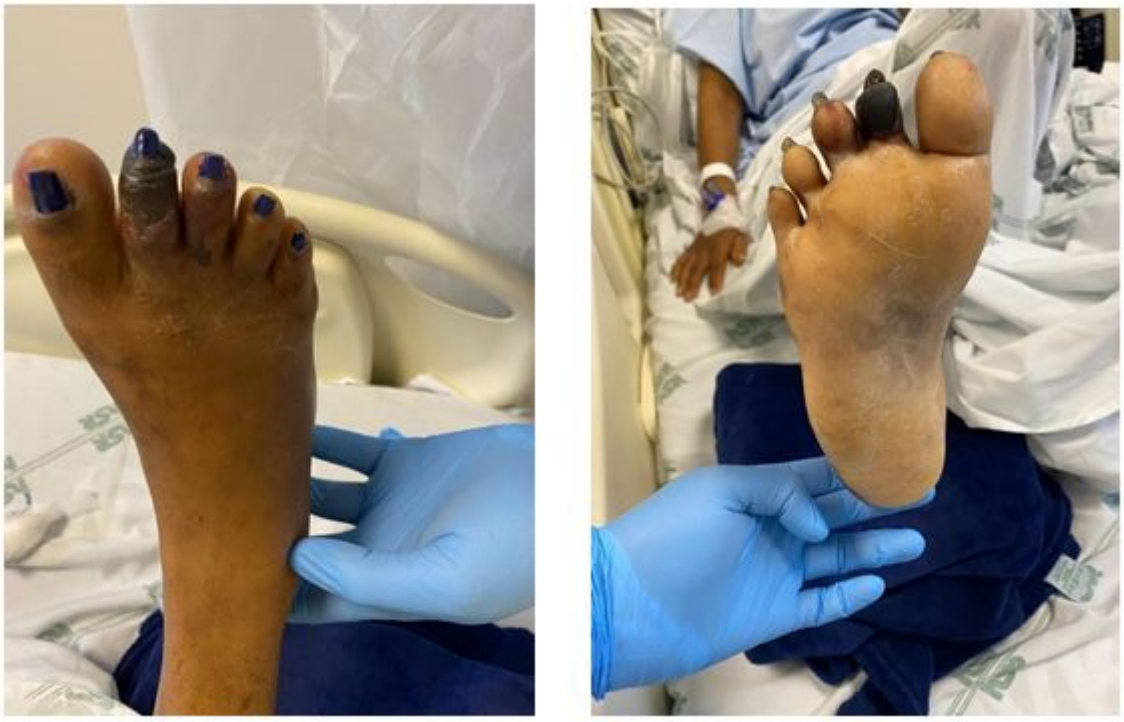

Figure 2

Right second toe arterial ischemia