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Acute COVID-19 induced fulminant systemic vascular thrombosis: A novel entity.

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Acute COVID-19 induced fulminant systemic vascular thrombosis: A novel entity

To the editor,

Coronavirus disease 2019 (COVID-19) has been implicated in the etiology of deep venous thrombosis, stroke and pulmonary embolism [1–3]. Here, we invoke a new variant of coagulopathy, acute COVID-19 induced fulminant systemic vascular thrombosis (ACoFSVT) characterized by a rapid, widespread, massive peripheral arteriovenous coagulopathy.

A 74-year-old male with a past medical history of Diabetes Mellitus (DM) presented with lethargy and hypoxia since one day prior. Additional history was limited, given his altered mental status.

In the emergency department (ED), he was febrile (39.1 celsius), tachycardic and tachypneic (respiratory rate 40 breaths per minute). His blood pressure was 75/50 mmHg. Arterial oxygen saturation was 44% requiring emergent intubation and mechanical ventilation. Electrocardiogram (EKG) demonstrated sinus tachycardia and a chest X-ray revealed bilateral interstitial infiltrates. He received vigorous intravenous fluid resuscitation followed by inotropic support with norepinephrine infusion. Given concerns for sepsis, broad-spectrum antibiotics were also initiated.

Initial laboratory investigation revealed prerenal azotemia (blood urea nitrogen 121 mEq/L, creatinine 3.59 mg/dl), hypernatremia (154 mEq/L), hyperkalemia (6.4 mEq/dL), and rhabdomyolysis Creatine Kinase (4673 U/L). His serum d-dimer level, C-reactive protein (CRP), and lactate dehydrogenase (LDH) were elevated at 69,000 ng/mL, 199 mg/dL and 910U/L, respectively (Fig. 1). The following day, a real-time polymerase chain reaction for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) returned positive. He was initially treated with hydroxychloroquine but this was later discontinued due to QT prolongation and short bursts of nonsustained ventricular tachycardia. Interleukin-6 (IL-6) inhibitors could not be utilized given his raised aminotransferase levels (450 IU/L), alanine aminotransferase (540 IU/L) and thrombocytopenia. The latter also precluded us from starting empiric therapeutic anticoagulation.

On day-2, he developed bilateral lower extremity edema, prompting venous imaging of the lower extremities. Doppler ultrasound (DUS) revealed widespread occlusive thrombosis in the right femoral and bilateral popliteal veins. DUS of the upper extremities also revealed occlusive thrombi in the right cephalic and left basilic vein. He was immediately started on therapeutic intravenous unfractionated heparin.

Two days later, he developed skin mottling and discoloration on the bilateral lower extremities and peripheral pulses could not be elicited. An arterial DUS of the lower extremities demonstrated massive occlusive thrombi in the bilateral common femoral, profunda femoris, superficial femoral, posterior tibial, peroneal and posterior tibial arteries. (Fig. 2) Given the extensive clot burden, anticoagulant was switched to argatroban, fearing heparin failure and considering the remote possibility of Heparin-induced thrombocytopenia. An extensive hypercoagulability workup comprising heparin-induced thrombocytopenia antibody testing, lupus anticoagulant (DRVVT), anticardiolipin antibody and beta-2-glycoprotein were negative. The rapidly progressing ischemia on anticoagulants, and bilateral lower extremities involvement was concerning for non-viable limbs.

After introspection with hematology, vascular surgery, and the family, it was decided that he would be a poor candidate for both for catheter-directed thrombolysis or vascular bypass surgery. Surgical intervention with emergent bilateral femoral endarterectomy followed by thrombectomy were attempted, however he eventually needed above knee lower extremity amputations. The hospital course was further complicated by persistent fevers, rhabdomyolysis, diffuse coagulopathy and a urinary tract infection in conjunction with COVID-19. Given his clinical deterioration, his family eventually opted to proceed with comfort directed care and transfer to a hospice facility.

The novel COVID-19 is a generation-defining global pandemic; the scale, scope and pace of which is unprecedented. The statistics to date are staggering. As of April 30, 2020, more than 3million confirmed cases from over 180 countries and more than 233,000 deaths had been documented worldwide. The estimated case burden in the US alone is expected to be 2–3 million. Given this, the mounting toll of COVID-19 related systemic and vascular complications requiring critical interventions could be daunting.

SARS-CoV-2 infection can elicit an intense inflammatory response by recruiting multiple cytokines and chemokines (IL-6, tumor necrosis factors), leading not only to direct endothelial injury but also to diffuse vascular inflammation. The Endothelial dysfunction seems to be mediated via viral infection of the endothelial cell. Also the impaired systemic microcirculatory functioning, vasoconstriction, stasis of blood flow during immobilization, changes in circulating prothrombotic factors during active infection may all potentiate this procoagulant state [2,4]. COVID-19 induced hypoxia, immobilization and reactive thrombocytosis, can also precipitate multivessel thrombosis [5]. Contemporary studies have shown that the degree of thrombosis may correlate with titers of coagulation biomarkers. Elevated levels of d-dimer have been shown to directly correlate with higher Sequential Organ Failure Assessment (SOFA) scores and worse clinical outcomes [6]. A multivariable regression has also shown increased odds of poor prognostic factors associated with d-dimer level greater than 1 μg/mL (18·42, 2·64–128·55; p = 0·0033) [4].

In our case, irrespective of the endothelial injury, the collision of COVID-19 induced direct vascular thrombosis, inherent to the disease-specific hypercoagulable state, and possible vasculopathy, due to long-standing diabetes triggered vascular occlusion. The

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Day of Illness	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Fever	101	100.7	101.6	100.2	100.9	100.7	101.8	100	101.1	100.2	102.1	101.8	100.2	
BP	75/50	128/91	125/98	109/70	103/62	111/65	123/63	111/61	114/60	130/91	134/88	101/56	136/82	
Heart Rate	124	91	106	93	77	83	83	88	119	106	101	92	76	
Ventilation	MV	MV	MV	MV	MV	MV	MV	NC	NC	NC	NC	NC	NC	NC
PEEP	10	10	10	5	5	5	5							
FIO2/Flow	80%	60%	40%	40%	40%	40%	40%	6L	6L	5L	3L	3L	2L	
Urea	121	117	55	50	48	45	41	39	38	34	30	24	20	
Creatinine	3.59	2.59	1.44	1.75	2.0	1.95	1.84	1.59	1.58	1.46	1.48	1.31	1.27	
D-Dimers	>69000	>69000		7154		971	2335		3300		2693			
Fibrinogen		923		420	615	504	710	710	615	632	569			
CRP	199		360			264		1188	334		236			
Ferritin			836	613	719	823		294	1390		1547			
LDH	910			1040	945	780		601	543	555	500			
CK	4673	5997		20402	15532	10938	7604						3362	
WBC	9.1	9.4	9.6	9.7	10.3	9.0	8.7	10.1	11.8	10.6	10.3	11.7	13.0	
Platelets	120	64	69	73	77	84	111	123	161	174	196	215	205	
	April 12	April 13	April 14	April 15	April 16	April 17	April 18	April 19	April 20	April 21	April 22	April 23	April 24	April 25

Fig. 1. In-hospital course, vitals and lab findings (yellow indicates on presser support, highlighted areas are abnormal values, MV: Mechanical Ventilation, NC: Nasal Cannula). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

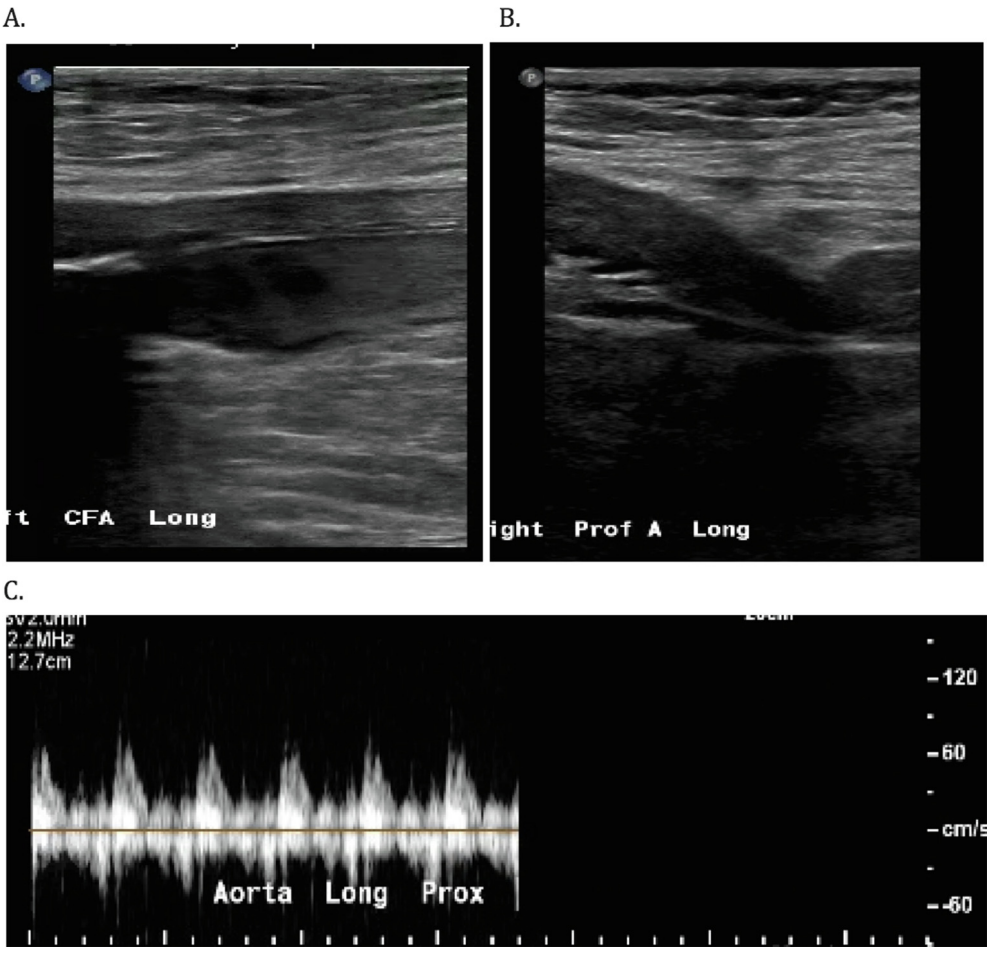

Fig. 2. (A) Left common femoral and (B) profunda femoris artery with a large occluding thrombus in the lumen and negative biphasic flow on Doppler ultrasound. (C) Biphasic flow waveform demonstrating absence of blood flow below proximal part of the femoral artery.

rise in d-dimer levels tracked with inflammatory biomarkers (CRP), reflecting both coagulopathy and vascular inflammation, a cause for acute COVID-19 related fulminant systemic vascular thrombosis (ACoFSVT). While a constellation of multiple mechanisms incited ACoFSVT, the resulting rhabdomyolysis, electrolyte disturbance and kidney failure further complicated the clinical course of our patient.

Although pathologically unproven, the dramatic cratering clinical trajectory of our patient despite being on therapeutic heparin also suggests that ACoFSVT severely disrupts normal homeostatic mechanisms, exhausting anticoagulant factors and leading to unopposed clotting pathway activation. This, especially in the setting of possible pre-existing endothelial dysfunction due to DM, precipitated widespread thrombosis [6]. One can also argue that lack of definitive treatment for COVID-19 and possible delay in the administration of heparin infusion due to thrombocytopenia on presentation might have contributed to the development of ACoFSVT. Regardless, it is imperative to identify early clinical risk factors such as baseline medical conditions that predispose to vasculopathy, significant elevated inflammatory markers and in particular high levels of d-dimer, and adopt an individualized approach to initiation of early therapeutic anticoagulation in these patients.

While remarkable efforts to unravel further management of acute COVID-19 related thrombotic complications are ongoing, we advocate for early recognition and timely anticoagulation in patients with high-risk features suggestive of ACoFSVT.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100620.

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