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Zain Ali  
*Abington Jefferson Health, PA, United States*

Waqas Ullah  
*Abington Jefferson Health, PA, United States*

Rehan Saeed  
*Abington Jefferson Health, PA, United States*

Ammar Ashfaq  
*Abington Jefferson Health, PA, United States*

Bilal Lashari, MD  
*Abington Jefferson Health, PA, United States*

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Ali, Zain; Ullah, Waqas; Saeed, Rehan; Ashfaq, Ammar; and Lashari, MD, Bilal, "Acute COVID-19 induced fulminant systemic vascular thrombosis: A novel entity." (2020). *Abington Jefferson Health Papers*. Paper 33.  
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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 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
**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.)

| 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 | 5 | 5 | 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 | 7154 | 7154 | 7154 | 7154 | 7154 | 7154 | 7154 | 7154 | 7154 | 7154 |
| **Fibrinogen** | 923 | 420 | 615 | 504 | 710 | 710 | 615 | 632 | 569 | 569 | 569 | 569 | 569 |
| **CRP**        | 199 | 360 | 264 | 1188 | 334 | 236 | 199 | 360 | 264 | 1188 | 334 | 236 | 199 |
| **Ferritin**   | 836 | 613 | 719 | 823 | 294 | 1390 | 1547 | 1547 | 1547 | 1547 | 1547 | 1547 | 1547 |
| **LDH**        | 910 | 1040 | 945 | 780 | 601 | 543 | 555 | 500 | 910 | 1040 | 945 | 780 | 601 |
| **CK**         | 4673 | 5997 | 28402 | 15532 | 10938 | 7604 | 1362 | 1362 | 1362 | 1362 | 1362 | 1362 | 1362 |
| **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 |

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**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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Zain Ali
Waqas Ullah *
Rehan Saeed
Ammar Ashfaq
Bilal Lashari
Abington Jefferson Health, PA, USA
* Corresponding author at: 1200 Old York Road, Abington, PA, USA.
E-mail address: waqasullah.dr@gmail.com (W. Ullah).
Received 10 May 2020
Received in revised form 23 July 2020
Accepted 10 August 2020
Available online 14 August 2020