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Don't forget arterial thrombosis in patients with COVID-19: A case series

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ABSTRACT

Introduction: The acute disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS COV-2) is accompanied by a hypercoagulable state. Multiple publications have described the venous thromboembolic events associated with coronavirus disease 2019 (COVID-19) but arterial thromboembolic events have yet to be described.

Cases description: We describe five COVID-19 patients that developed severe morbidity as a result of occlusive arterial thromboembolic events occurring despite treatment with low molecular weight heparin. All cases presented with an acute confusional state and were accompanied by rapid elevations of lactate and D-dimers and leukocytes. The end organs involved were the kidneys, spleen, liver, lungs, central nervous system, intestines and limbs. Only one of the five patients survived.

Conclusion: COVID-19 is associated with not only venous but also arterial thromboembolic events. Further research is required to clarify the incidence, causes and possible modes of prevention of this potentially lethal disease complication.

1. Introduction

The hypercoagulable condition accompanying COVID-19 patients has been reported extensively and is associated with high morbidity and mortality [1,2]. The literature describes mainly venous thromboembolic events (VTE) and pulmonary embolism [3,4]. Yet patients with COVID-19 have been described to suffer high rates of venous thrombosis despite anticoagulation [5]. Recently these phenomena have been proposed to occur due to thrombosis in situ rather than discrete embolic events [6]. Attention has thus far been focused on venous thromboembolic events in this context and administration of anticoagulants is largely targeted to prevent this process. We present five critically ill patients with COVID-19 that developed severe morbidity as a result of occlusive arterial thromboembolic events occurring despite treatment with low molecular weight heparin. (see Figs. 1 and 2)

2. Case descriptions (Table 1)

Case 1. initially received home therapy following diagnosis with COVID-19 but nine days after symptoms onset and six days after diagnosis he was referred to the hospital due to worsening diffuse abdominal pain and constipation. His physical examination revealed a slightly tender abdomen with no signs of peritonitis. Computed tomography (CT) was performed due to elevated lactate levels and revealed bilateral complete occlusion of both renal arteries, the superior mesenteric artery and the celiac trunk.

Case 2. was hospitalized due to worsening symptoms one week after diagnosis. Despite treatment with therapeutic-dose LMWH, increasing hypoxemia led to endotracheal intubation and veno-venous extracorporeal mechanical oxygenation (ECMO) with therapeutic heparinization (activated clotting time 180–220 seconds). Shortly thereafter the patient developed culture negative hemodynamic instability and leukocytosis and was sent to CT which revealed extensive thrombosis of the aorta, celiac trunk, hepatic and splenic arteries.

Case 3. was hospitalized with worsening respiratory symptoms and was intubated eight days after admission despite treatment with therapeutic-dose LMWH and non-invasive respiratory support. Post

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19; coronavirus disease 2019, CT; computed tomography; ED, emergency department; LMWH; low molecular weight heparin; SARS COV-2, severe acute respiratory syndrome coronavirus 2; VTE, Venous thromboembolic event.

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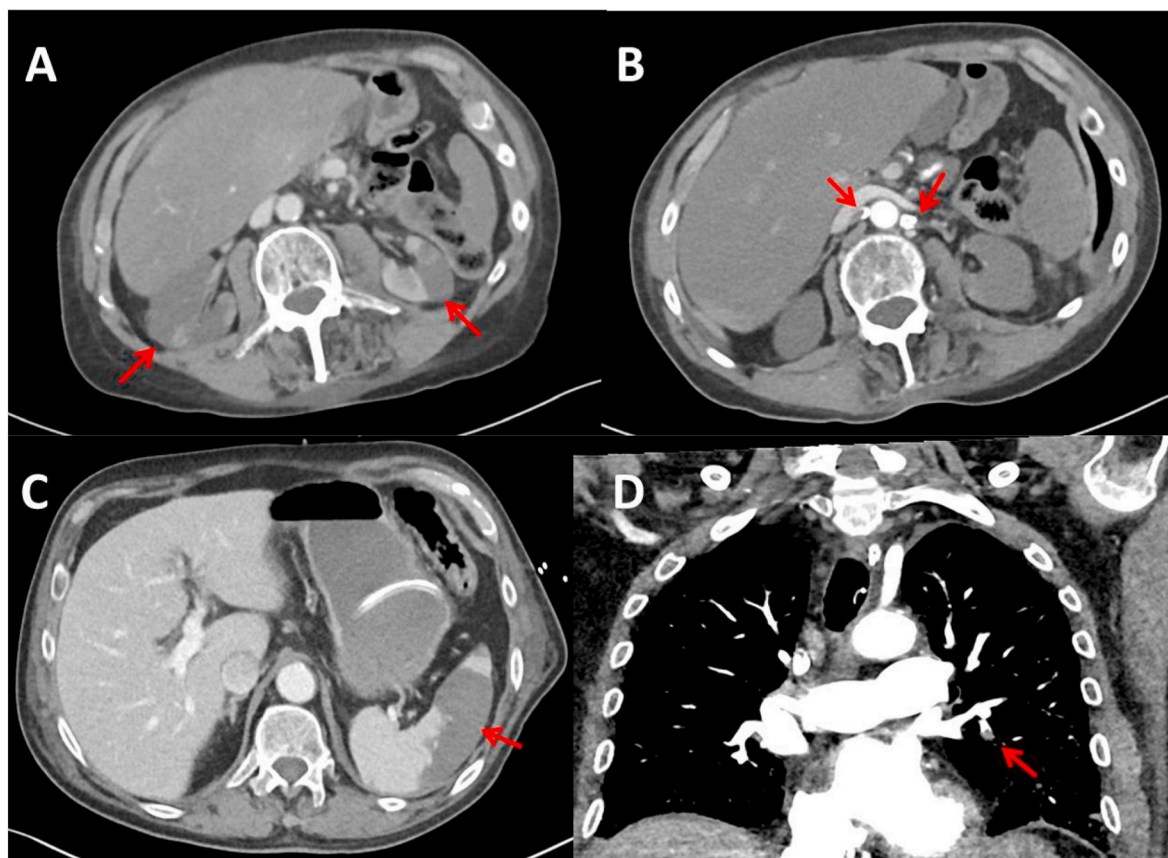


Fig. 1. Thromboembolic events demonstrated in CT scans of patients 1 (A,B) and 4 (C,D). A- Bilateral renal infarcts B - Bilateral renal artery occlusion C – Splenic infarct D – Left lower lobe segmental PE.

intubation, electrocardiography revealed inferior-lateral ST segment elevation and blood tests showed increasing troponin levels. Treatment with heparin and dual antiplatelet therapy was initiated. Worsening hemodynamic instability, elevated lactate and white cell counts led to performance of CT which revealed extensive brain, lung, spleen and kidney infarctions.

Case 4. underwent intubation three days after admission due to severe hypoxemia and cognitive impairment despite therapeutic-dose LMWH. On the day after intubation physical examination revealed a cold and discolored left hallux. Dorsalis pedis and posterior tibial pulses were normal. However, blood lactate levels and the white cell count increased and the patient was therefore sent to a CT scan that showed lung, spleen and kidney infarctions.

Case 5. had been discharged from another hospital after convalescing from COVID-19. Three days after discharge he began to suffer from left forearm pain, paresthesias and discoloration which led him to self-refer to our ED. Physical examination revealed tender, pale and cold left arm and fingers. Doppler examination diagnosed occluded radial and ulnar arteries. Urgent vascular surgery revealed multiple thromboses in the brachial, radial and ulnar arteries. The thrombi were removed with a Fogarty catheter, arterial flow was reestablished with evidence of good reperfusion and the patient was referred to a completion CT scan.

All of the presented patients manifested with life or limb threatening

arterial occlusions despite treatment with LMWH (see [Table 1](#)) and four of these five patients did not survive the event.

3. Discussion

Mortality from COVID-19 occurs mainly due to pulmonary disease involvement. However, contrary to classical acute respiratory distress syndrome (ARDS), which involves the alveolar component of the lung, the pulmonary damage of COVID-19 has both alveolar and vascular occlusive elements [2]. Publications describing the pro-thrombotic state in critically-ill COVID-19 patients have also led to the realization that these vascular occlusions are a systemic rather than a local pulmonary phenomenon. Approximately one third of hospitalized critically-ill patients with COVID-19 develop thrombotic complications, mostly VTEs but also ischemic strokes and myocardial infarctions [7]. Autopsies of deceased COVID-19 patients found micro-angiopathy and thrombosis in the lungs [8] and cases of arterial thrombosis causing mesenteric ischemia have also been reported [9].

This series included patients that arrived from home with the arterial thrombotic event as their initial presentation as well as patients already critically ill at the time thrombosis was diagnosed. The threshold for performing computed tomography imaging should therefore be low for outpatients presenting with elevated lactate levels and leukocytosis and inpatients with sudden obtundation.

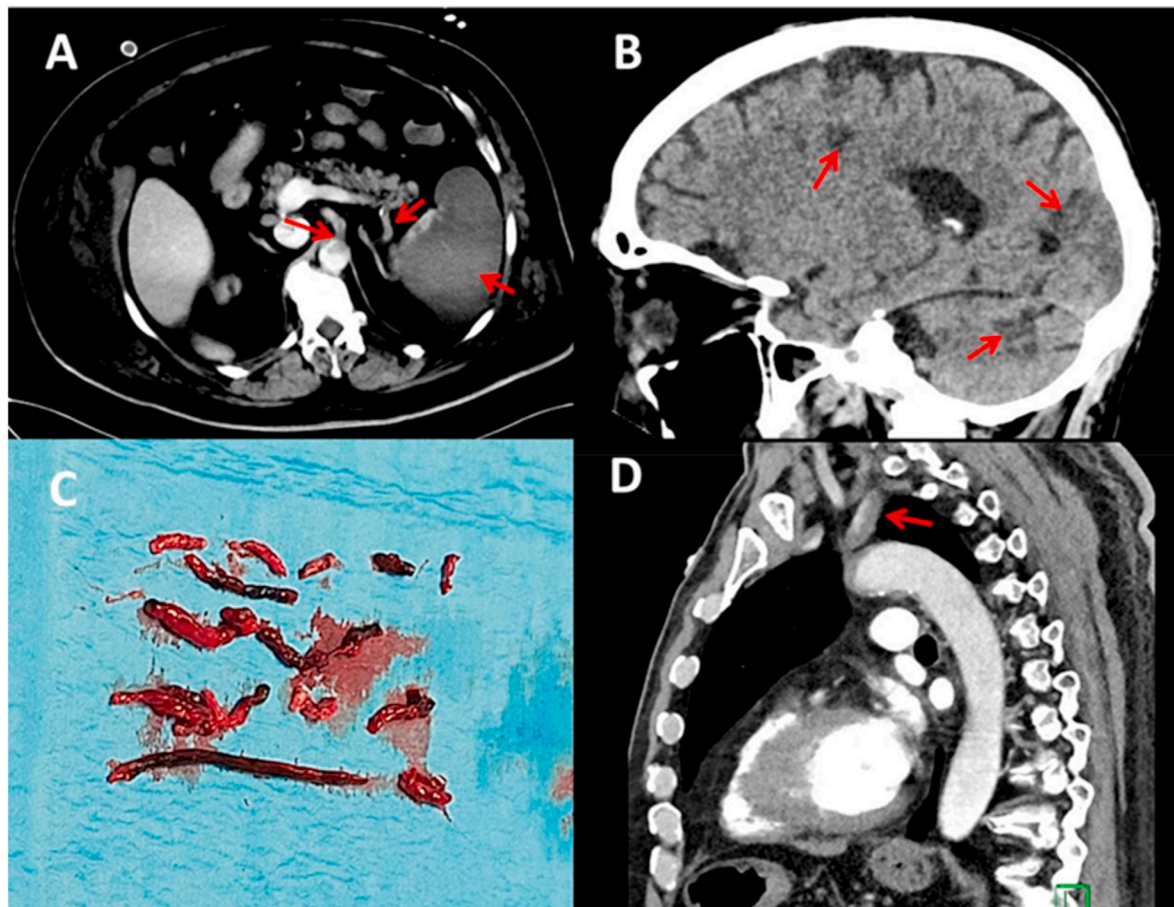


Fig. 2. Thromboembolic events of patients 2,3,5. **A**– Abdominal CT angiography of patient 2 demonstrating celiac trunk and splenic artery thrombosis and splenic infarct. **B** Brain CT scan of patient 3 demonstrating multiple supra and infra-tentorial brain infarcts **C**–Thromboses extracted from the brachial, radial and ulnar arteries of patient 5 **D** – Chest CT scan of patient 5 showing left subclavian artery thrombosis.

The cytokine storm that accompanies the response to SARS-CoV-2 infection may activate the coagulation system, cause endothelial damage and release tissue factors [10,11]. A correlation has been observed between D-dimer and fibrinogen levels and the levels of pro-inflammatory cytokine IL-6 in patients with severe COVID-19 [12]. Although both venous and arterial thrombi are affected by inflammation and the immune system, there are important differences between the two.

Venous thrombosis typically stems from diminished venous flow, endothelial injury and a hypercoagulable state. Plasma fibrinogen, factor VIII and antiphospholipid antibody levels are often elevated in severe COVID-19 patients, while anti-coagulant factors such as anti-thrombin, protein C and protein S are decreased [13]. All of these constitute evidence of a hypercoagulable state and probably contribute to the increased risk of venous thrombosis in COVID-19.

Arterial thrombosis occurs in a rapid blood flow environment and often occurs after an atherosclerotic plaque rupture or vascular injury that exposes thrombogenic elements to the blood. Platelets, which possess unique adherence capabilities in high shear forces, are a major contributor to arterial thrombosis [14]. Changes in platelet function, found in COVID-19 patients, might explain these arterial thrombotic events. Platelets are activated at lower thresholds than normal in COVID-19 patients [15], and an increase in platelet aggregate formation

has also been shown [16]. COVID-19 patients may therefore benefit from antiplatelet treatment.

Several studies have noted that treatment with aspirin before diagnosis with COVID-19 may correlate with favorable outcomes; milder disease, less ICU admission and reduced mortality rates [17–19]. Mortality was also lower among COVID-19 patients who received aspirin during hospitalization [20]. However, while this evidence would seem to suggest a possible beneficial effect of aspirin, all of these studies were retrospective which precludes drawing conclusions regarding causation.

This case series adds to the emerging evidence of diffuse systemic arterial occlusion in COVID-19 patients, often despite therapeutic anticoagulation. It raises important questions regarding the physiological processes underlying this disease component and whether it is at all preventable with standard anticoagulation or antiplatelet regimens.

Clinicians tend to extrapolate from prior knowledge and experience. It was misleading to believe the pulmonary manifestations of COVID-19 are similar to classic ARDS as this led to the belief that we can save patients solely by treatment of the pulmonary disease. It may be similarly misleading to believe the thromboses observed in COVID-19 stem from a classic prothrombotic state; precious time that could have been used to seek the cause of this condition may be lost when trying to prove we can save lives with anticoagulation alone.

Table 1
Characteristics and laboratory analysis of the presented five patients with severe COVID-19.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age	68	59	70	78	58
Sex	Male	Male	Male	Male	Male
BMI	–	30	24.5	25	28.5
Medical history	None	HTN, DM, hyperlipidemia	None	HTN	DM, prior DVT after neck of femur fracture
Symptoms before diagnosis	weakness, fever, dyspnea, diffuse abdominal pain, constipation	fever, cough, dyspnea	fever, cough, loss of appetite	fever, cough, dyspnea	fever, cough, dyspnea, anosmia
Days of symptoms before admission	9	7	2	4	12
Medications before admission					
Respiratory support	Acute home oxygen therapy	–	–	–	Non-invasive respiratory support in another hospital until withdrawal
Steroids	–	–	–	–	Dexa
Anti-platelet	–	–	–	Aspirin	–
Anti-coagulation	LMWH- Prophylactic dose	–	–	–	LMWH - Intermediate dose
Body temperature on admission	36.5	38.2	36.9	38.2	36.9
Room air saturation on admission (%)	80	64	94	64	94
Blood tests on admission					
Platelets (x10⁹/l)	274	168	189	233	323
Leucocytes (x10⁹/l)	15.6	5.1	8.2	8.5	16.8
Lymphocytes (x10⁹/l)	0.53	1.17	0.64	0.34	4
CRP (mg/dL)	24	11.6	21	29	0.59
D-dimer (ng/ml)	109189	577	1449	1856	1098
Lactate (mmol/L)	13	1.5	2	–	2.4
Medications on admission					
Steroids	Dexa	Dexa	Dexa	Dexa	Dexa
Anti-platelets	–	–	–	Aspirin	–
Anti-coagulation	–	LMWH - therapeutic dose	LMWH - therapeutic dose	LMWH - therapeutic dose	–
Days from admission to event	–	10	8	4	–
Blood tests on day of event					
Platelets (x10⁹/l)	274	236	91	139	323
Leucocytes (x10⁹/l)	15.6	38.6	32.6	17.6	16.8
Lymphocytes (x10⁹/l)	0.53	4.4	0.54	0.7	4
C reactive protein (mg/dL)	24	14.3	16.5	29	0.59
D-dimer (ng/ml)	109189	3270	50074	19041	1098
Fibrinogen (mg/dL)	520	627	349	454	469
INR	2.21	0.96	1.7	1.33	1
hsTroponin (ng/L)	41	84	2900	4368	6
Lactate (mmol/L)	13	1.7	6.6	3	2.4
Autoantibodies					
Anti-Beta 2GP1 IgG	weakly positive	negative	negative	negative	negative
Anti Cardiolipin IgM	negative	negative	negative	negative	negative
anti Cardiolipin IgG	negative	negative	negative	negative	negative

(continued on next page)

Table 1 (continued)

	Case 1	Case 2	Case 3	Case 4	Case 5
Computed tomography findings	Segmental and sub-segmental pulmonary embolism in the upper and lower lobes of the left lung, bilateral complete occlusion of both renal arteries, the superior mesenteric artery and the celiac trunk, large spleen, liver and renal infarctions	Extensive thrombosis of the descending thoracic and abdominal aorta, celiac trunk, hepatic artery, splenic artery and splenic vein; spleen and right kidney infarctions	Multiple supra- and infra-tentorial brain infarctions, vascular occlusion of sub-segmental areas of both lungs; spleen and kidney infarctions	Multiple bilateral segmental and sub-segmental pulmonary emboli with lung infarctions; spleen and bilateral kidney infarctions	(Post-surgery) Proximal thrombosis with near complete occlusion of the left subclavian artery despite good distal filling; segmental right upper lobe pulmonary embolism
Anti-coagulation after CT	Heparin	Heparin	LMWH - therapeutic dose	LMWH - therapeutic dose	Heparin
Outcome	Deceased 2 days after event	Deceased from sepsis 1 month after event	Deceased 2 weeks after event	Deceased 3 days after event	Regained good sensory and motor function of the operated hand

Abbreviations: HTN – hypertension, DM – diabetes mellitus, DVT – deep vein thrombosis, DVT – deep vein thrombosis, LMWH – low molecular weight heparin.

Prior abstract publication/presentation

None.

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.

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