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Short communication

Unusual arterial thrombotic events in Covid-19 patients

C. de Roquetaillade [a,b,*], B.G. Chousterman [a,b,c], D. Tomasoni [d], M. Zeitouni [e], E. Houdart [f], A. Guedon [f], P. Reiner [g], R. Bordier [a], E. Gayat [a,b,c], G. Montalescot [e], M. Metra [d], A. Mebazaa [a,b,c]

[a] Department of Anesthesiology and Critical Care, Hôpital Lariboisière (AP-HP), Paris, France
[b] Inserm U942 MASCOT, Paris, France
[c] Université de Paris, Paris, France
[d] Cardiothoracic Department, Civil Hospitals and University of Brescia, Brescia, Italy
[e] Sorbonne Université, Action Study Group, Institut de Cardiologie, Hôpital Pitié-Salpêtrière (AP-HP), Paris, France
[f] Departments of Interventional Neuroradiology, Hôpital Lariboisière (AP-HP), Paris, France
[g] Department of Neurology, Hôpital Lariboisière (AP-HP), Paris, France

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ABSTRACT

Introduction: COVID-19 infection is commonly complicated with pro-thrombotic state and endothelial dysfunction. While several studies reported a high incidence of venous thromboembolic events. The occurrence of arterial thromboses are yet rarely described and could be underestimated.
Objectives: To describe the clinical and biological characteristics of COVID-19 patients presenting with an associated arterial thromboembolic event.
Material and methods: We performed a retrospective multicentric study in 3 centers between France and Italy. All patients with a confirmed SARS-CoV-2 infection and arterial thromboembolic events were included in the analysis.
Results: From March 8th to April 25th 2020, we identified 20 patients (24 events) with arterial thromboembolic events over 209 admitted patients (9.6%) with severe COVID-19 infection. Arterial thrombotic events included acute coronary occlusions ($n = 9$), stroke ($n = 6$), limb ischemia ($n = 3$), splenic infarcts ($n = 3$), aortic thrombosis ($n = 2$) and occlusive mesenteric ischemia ($n = 1$). At the time of the event, 10/20 (50%) of patients received thromboprohylaxis, 2/20 (10%) were receiving treatment dose anticoagulation and 5/20 (25%) were receiving antiplatelet therapy.
Conclusion: Our observations suggest that serious arterial thrombotic events might occur in Covid-19 patients. However, the exact incidence of such events and the best way to prevent them yet remains to be investigated.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is commonly complicated with pro-thrombotic state and endothelial dysfunction [1]. Excess of venous thromboembolic events (deep vein thrombosis (DVT), pulmonary embolism (PE)) have been described among patients suffering from coronavirus disease 2019 (Covid-19) [2]. However, arterial thrombosis are yet rarely described in this setting and could be underestimated [3]. Here we report our multicentric experience with patients suffering from arterial thromboembolic events during the first months of the Covid-19 outbreak in Western Europe.

2. Material and method

During a six weeks period (March 8th to April 25th 2020) we performed a retrospective study in three critical care departments. Patients with a confirmed SARS-CoV-2 infection (rt-PCR) and arterial thromboembolic events were included in the analysis. Baseline characteristics, biological findings and imaging were extracted from medical records. For most patients, antithrombotic prophylaxis was made of 4000UI per day of enoxaparine administered subcutaneously, the dose was increased (6000UI/day or 8000UI/day) in case of obesity (BMI > 30 kg/m^2). In patient treated with therapeutic dose anticoagulant, the therapeutic objectives followed international recommendations (AntiXa activity 0.3–0.6 for unfractionated heparin (UFH), and no systematic AntiXa monitoring for low-molecular-weight heparin (LMWH) treatment except for patient at risk of altered renal function or obese or unstable patients, for those the AntiXa was monitored and the LMWH doses were adapted for an AntiXa activity between 0.5 and 1.2 UI/mL). For the descriptive analysis, continuous variables were expressed as median (interquartile range) and categorical variables as numbers (percentages). This study was approved by our local committee (Institutional Review Board -IRB 00006477- of HUPNVS, Paris 7 University, AP-HP).

* Corresponding author: Inserm U942 MASCOT, Université de Paris, Hôpital Lariboisière - Bâtiment Viggo Petersen, 41, boulevard de la Chapelle, 75475 Paris Cedex 10, France.
E-mail address: charles.de-roquetaillade@aphp.fr (C. de Roquetaillade).

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Table 1
Characteristics of 20 patients with Covid-19 with arterial thrombotic event.

Characteristics	All	ACS	Stroke	Other[1]
	$n = 20$/number available	$n = 9$	$n = 6$	$n = 5$
Median age, year (interquartile range)	62 (58–70)	60 (57–71)	59 (52–67)	65 (62–71)
Male sex, *n* (%)	15 (75)	6 (67)	4 (67)	5 (100)
Ethnicity				
Caucasian, *n* (%)	13 (65)	7 (78)	4 (67)	2 (40)
Sub-Saharan African, *n* (%)	7 (35)	2 (22)	2 (33)	3 (60)
Cardiovascular risk factors				
Hypertension, *n* (%)	14 (70)	6 (67)	3 (50)	5 (100)
Dyslipidemia, *n* (%)	5 (25)	3 (33)	2 (33)	0 (0)
Diabetes mellitus, *n* (%)	4 (20)	1 (11)	2 (33)	1 (20)
Obesity, *n* (%)	3 (15)	0 (0)	2 (33)	1 (20)
Peripheral artery disease, *n* (%)	2 (10)	0 (0)	1 (17)	1 (20)
COPD, *n* (%)	1 (5)	0 (0)	0 (0)	1 (20)
Previous DVT or PE, *n* (%)	1 (5)	1 (11)	0 (0)	0 (0)
Myocardial infarction, *n* (%)	4 (20)	3 (33)	1 (17)	0 (0)
Prior stroke, *n* (%)	1 (5)	1 (11)	0 (0)	0 (0)
≥2 risk factors	9 (45)	4 (44)	3 (50)	2 (40)
Chronic medication				
ACEi/ARB, *n* (%)	8 (40)	3 (33)	1 (17)	4 (80)
Aspirin, *n* (%)	4 (20)	3 (33)	0 (0)	1 (20)
P2Y12 inhibitor, *n* (%)	2 (10)	1 (11)	1 (17)	0 (0)
Anticoagulant, *n* (%)	1 (5)	1 (11)	0 (0)	0 (0)
Motif of admission				
Shortness of breath, *n* (%)	9 (45)	3 (33)	3 (50)	3 (60)
Fever, cough, *n* (%)	5 (25)	1 (11)	2 (33)	2 (40)
Ischemia related symptom, *n* (%)	5 (25)	4 (44)	1 (17)	0 (0)
Characteristic on admission				
SAPS II	33 (23–66)	36 (30–63)	23 (18–68)	27 (25–65)
SOFA	2 (2–9)	2 (1–4)	3 (2−12)	3 (2−11)
Charlson comorbidity score	2 (1–3)	1 (1–1)	1 (1–3)	1 (1–4)
Patient under mechanical ventilation, *n* (%)	5 (25)	1 (11)	2 (33)	2 (40)
P/F ratio	200 (128–294)/15	308 (222–342)/4	188 (156–260)	168 (106–233)
Median Laboratory values at time of event (median, interquartile range, n*)*				
White cell count, $\times 10^{-3}/mm^3$	11.9 (8.1–14.0)/20	12.3 (5.4–13.2)	10.3 (7.5–12.3)	12.9 (11.4–16.9)
Neutrophils, $\times 10^{-3}/mm^3$	10.2 (8.7–10.7)/17	9.5 (4–11.7)	8.9 (8.6–9.4)	12.1 (10.5–14.8)
Lymphocytes, $\times 10^{-3}/mm^3$	1.03 (0.84–1.5/18	1.1 (0.9–1.3)	0.9 (0.9–1.5)	0.9 (0.5–1.3)
Platelet, $\times 10^{-3}/mm^3$	294 (212–386)/19	262 (216–295)	382 (153–421)	324 (220–389)
Ferritin, μg/L	1162 (509–1857)/10	689 (537–951)/3	1270 (978–2231)/4	2000 (1225–2891)/3
CRP, mg/L	92 (22–146)/16	26 (16–146)	105v(73–127)/4	114 (69–277)/3
D-Dimer, ng/mL	2725 (848–4163)/20	890 (651–1429)	4700 (2867–7417)	3900 (3380–4204)
Fibrinogen, g/L	7.1 (5.0–7.4)/19	4.9 (3.6–6.7)	7.1 (6.6–7.1)	7.8 (5.8–8.8)/4
INR	1.12 (1.04–1.21)/20	1.1 (1.0–1.2)	1.1 (1.1–1.2)	1.4 (1.3–1.9)
aPTT	1.06 (0.91–1.1)/14	1.05 (1.03–1.09)/7	0.9 (0.8–1.0)/4	1.1 (0.9–4.3)/3
vW Factor activity, %	>200 (200−200)/3	–	–	>200 (200–200)/3
ADAMTS13 activity, %	68 (66–70)/2	–	–	68 (66–70)/2
AT III activity, %	108 (99–114)/4	–	–	113 (100–115)/3
FV Leiden or factor II mutation, *n* (%)	0 (0)/3	–	–	0 (0)/3
Lupic anticoagulant, *n* (%)	0 (0)/5	–	–	0 (0)/5
Anti-PF4 antibody, *n* (%)	0 (0)/3	–	–	0 (0)/3
Patent foramen ovale, *n* (%)	2 (10)/12	0 (0)/3	1 (17)/5	1 (20)/4
Treatment				
Antiplatelet therapy at time of event, *n* (%)	4 (20)	3 (33)	0 (0)	1 (20)
Anticoagulant at time of event, *n* (%)	12 (60)	7 (63)	2 (33)	3 (60)
Antibiotic, *n* (%)	14 (70)	6 (67)	5 (83)	3 (60)
Glucocorticoids, *n* (%)	4 (20)	1 (11)	2 (33)	1 (20)
Hydroxychloroquine, *n* (%)	11 (55)	4 (44)	4 (67)	3 (60)
Tocilizumab or other anti IL6, *n* (%)	1 (5)	0 (0)	1 (17)	0 (0)
Characteristic of thrombotic event				
Time from symptom onset, days	11 (7–13)	8 (4–10)	9 (7–12)	14 (13–25)
Time from hospital admission, days	0.5 (0–5)	0 (0–0)	3 (0–5)	7 (5–11)
Multiple arterial ischemic event	4 (20)	2 (22)**	2 (33)*	0 (0)
Associated PE or phlebitis, *n* (%)	6 (30)	1 (11)	2 (33)	3 (60)
Outcome				
pPCI	3 (15)	3 (33)	0 (0)	0 (0)
Thrombectomy, *n* (%)	4 (20)	0 (0)	3 (50)	1 (20)
Thrombolysis, *n* (%)	1 (5)	0 (0)	1 (17)	0 (0)
Mechanical ventilation, *n* (%)	9 (45)	3 (33)	2 (33)	3 (60)
AKI, *n* (%)	10 (50)	2 (22)	1 (17)	4 (80)
Hospital Mortality, *n* (%)	4 (20)	2 (22)	1 (17)	1 (20)

ACS: Acute coronary syndrome; COPD: Chronic Obstructive Pulmonary Disease; DVT: Deep Vein Thrombosis; PE: Pulmonary embolism; ACEi: angiotensine converting enzyme inhibitor; ARB: angiotensin receptor blocker; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; LMWH: Low Molecular Weight Heparin; UFH: Unfractionated Heparin; NOACS: New Oral Anticoagulant; PCI: Percutaneous coronary intervention; AKI: Acute Kidney Injury.

[1] Aortic thrombosis, ($n = 2$), acute limb ischemia ($n = 2$), splenic infarct ($n = 1$).

* One patient had concomitant limb ischemia, another patient had concomitant splenic infarct. No patent foramen ovale was retrieved among these patients.

** One patient had concomitant splenic infarct, another patient had concomitant mesenteric ischemia. No concomitant venous thromboembolism nor patent foramen ovale.

3. Results

We report a total of 20 patients out of a total of 209 patients (9.6%) observed of COVID-19 patients suffering from arterial thromboses. Among them 4 patients had multiple arterial thrombotic events, accounting for a total of 24 events (Table 1). A total of 5/20 (25%) patients had ischemia-related symptoms (sudden neurologic deficit or acute coronary syndrome) at the time of presentation and the other 15/20 patients developed ischemia during hospitalization. Reported arterial thrombotic events were acute coronary occlusions ($n = 9$), stroke ($n = 6$), limb ischemia ($n = 3$), splenic infarcts ($n = 3$), aortic thrombosis ($n = 2$) and occlusive mesenteric ischemia ($n = 1$). Four patients developped multiple arterial event during their stay. Those patient had no concomitant venous thromboembolism nor patent foramen ovale (PFO). Only two patients (one patient with stroke and one patient with splenic infarct) had associated PFO but no concomitant deep vein thrombosis nor pulmonary embolism. The majority (15/20) of patients were male, with a median age of 62 (interquartile range 58–70) years. The time from onset of symptoms to arterial thrombotic events was 11 (7–13) days. A total of 10/20 patients were receiving antithrombotic prophylaxis at the time of event (enoxaparine 4000UI/24 h ($n = 6$), 8000UI/24 h ($n = 3$), 6000UI/24 h ($n = 1$) and 2/20 patients were receiving treatment dose anticoagulation (one with UFH 20000UI/day and one with LMWH 6000UI × 2/24 h). 4/20 patients (20%) received aspirin and 2/20 (10%) were receiving PY214 inhibtor. Regarding therapeutic intervention, thrombolysis was attempted in one patient with stroke (failure), primary Percutaneous Coronary Intervention was successfully attempted in 3 patients with ST-segment elevation myocardial infarction, and thrombectomy was performed in 3 patients with stroke (1 failure, 2 successes). One patient underwent successful thrombectomy for acute limb ischemia, however, he presented a fatal relapse few days later. Surprinsingly, no patient was actively smoking at the time of the event.

At the time of event, the average levels of fibrinogen and D-Dimer were 7.1 (5.0–7.4) g/L and 2725 (848–4163) ng/mL, respectively. Six patients (30%) had a concomitant venous thromboembolic event (pulmonary embolism or lower limb DVT). All patients, except one, who was receiving curative anticoagulant, were in sinus rhythm. No patient had thrombocytopenia at the time of the event and median platelet count was of 294 (212–386) $\times 10^{-3}/mm^3$. anti-PF4 antibody research conducted in 3 patients was negative. ADAMTS13 activity tested in 2 patients was normal. A total of 4 patients (20%) died in the hospital, all from complications due to ischemia (extended aortic thrombosis ($n = 1$) (Fig. 1), mesenteric ischemia ($n = 1$), fatal cardiogenic shock ($n = 1$) and devastating brain injury ($n = 1$)).

4. Discussion

In this multicentric serie of patients, severe SARS-CoV-2 infection was complicated with atypical severe arterial thrombotic events including acute coronary infarction, stroke, and limb ischemia not prevented by thromboprophylaxis. Thromboses we observed occurred mainly on non-atherosclerotic vessels. Patients were of relatively young age and available CT-scans and angiography revealed no prior major atherosclerosis. Our observations suggest that a significative proportion of arterial thromboses in Covid-19 patients might occur over non diseased or mildly diseased vessels [4]. A prothrombotic state might be triggered by various mechanisms such as inflammation, endothelial injury or vascular injury [5]. Taken together, our observations suggest that serious arterial thrombotic events occur in Covid-19 patients who exhibit high

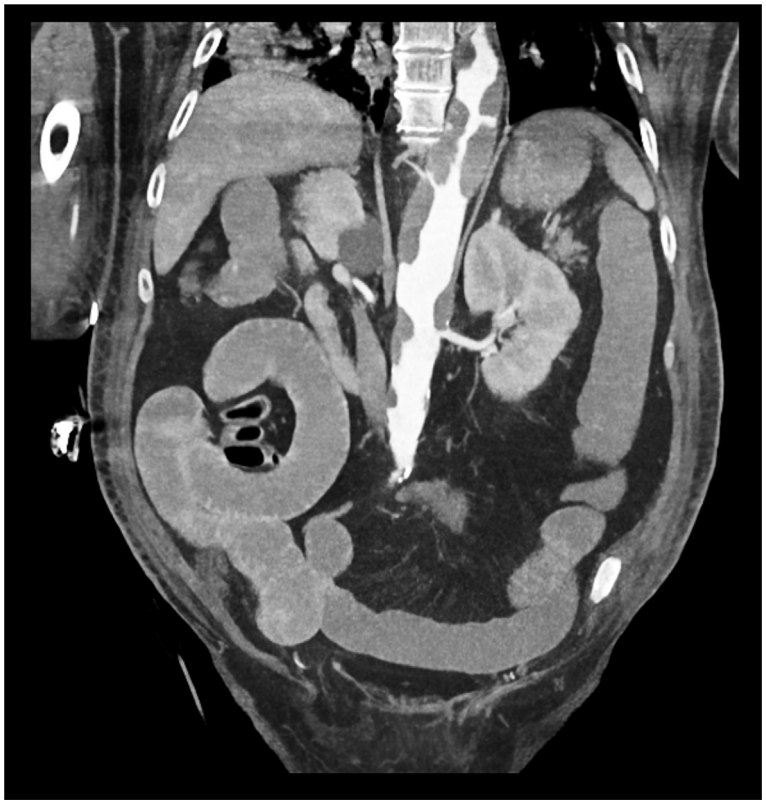

Fig. 1. Fatal aortic thrombosis in COVID-19 patient. Arterial-TDM showing extended intra-luminal aortic thrombi in a patient suffering from COVID-19. A 74 years old patient was admitted in ICU for respiratory failure. Nasal swab confirmed the suspected COVID-19. Doppler ultrasound revealed no deep venous thrombosis despite D-dimers >20000UI/L. The patient received prophylactic enoxaparin (4000UI/12 h). On the 6th day, the patient presented lower *limb* ischemia and abdominal occlusion syndrome. Subsequent Arterial-TDM revealed *de novo* multifocal and circumferential aortic thrombi of suprarenal and subrenal localization, with up to 50% occlusion on the infra-renal portion. There were no associated deep vein thrombosis nor pulmonary embolism.

inflammation and sometimes unusual localisation of these thrombotic events. Those arterial thromboses might be reason for admission but can also occur during hospitalization of patients with Covid-19. Several recommandations were emitted by several groups regarding VTE prevention and management [6] same as ACS occuring among Covid-19 patients [7]. However, the best prevention and management of arterial thromboses in the Covid-19 context remains to be elucidated.

Role and contribution of the authors

CdR Conceptualization; Data curation; Formal analysis, Writing - original draft. DT, MZ, AG, PR, RB, TM Data curation, Methodology, Writing - review and editing BGC, EH, EG, MM, GM and AM Supervision, Investigation, Writing - review & editing,

Declaration of Competing Interest

All authors declare no conflict of interest in relation with the present study.

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