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ORIGINAL ARTICLE

Aortic thrombosis as a dramatic vascular complication in COVID-19 disease

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Summary
Objective. — To report clinical outcomes of COVID-19 related acute aortic thrombosis (AAT).
Methods. — Consecutive COVID-19 patients presenting with AAT between April 2020 and August 2021 were included retrospectively. Clinical and radiological data were prospectively collected.
Results. — Ten patients (men, 90%; mean age, 64 ± 2 years) were included. At the time of AAT diagnosis, four patients were in intensive care unit. Median time between diagnosis of COVID-19 and AAT was 5 days [IQR 0—8.5]. Clinical presentation was acute lower limb ischaemia ($n = 9$) and mesenteric ischaemia ($n = 2$). Thrombus localization was the abdominal aorta ($n = 5$), the thoracic aorta ($n = 2$) or both ($n = 3$), with the following embolic sites: lower limbs ($n = 9$), renal arteries ($n = 3$), superior mesenteric artery ($n = 2$), splenic artery ($n = 1$), cerebral arteries ($n = 1$). Revascularization was performed in 9 patients, using open ($n = 6$), endovascular ($n = 2$) or hybrid techniques ($n = 1$). Three patients required reinterventions. The 30-day mortality was 30%. Three major amputations were performed in two patients, resulting in a free-amputation survival rate of 50% after a median follow-up of 3,5 months [IQR 2—4.1].
Conclusion. — AAT is a rare and devastating complication of COVID-19 disease, responsible for high mortality and amputation rates.

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Introduction

The severe acute respiratory syndrome coronavirus 2 (COVID-19) is associated with a high rate of venous and arterial thromboembolic events related to diffuse intravascular coagulation, excessive inflammation, hypoxia and immobilisation [1]. The pathophysiology of vascular complications in SARS-CoV-2 is related to the fact that the virus infects the host using the angiotensin converting enzyme 2 (ACE2) receptor. The ACE2 receptor, which is expressed in several organs such as the lungs, the heart, the kidneys and the bowel, is also expressed in endothelial cells, where viral inclusion structures have been observed [2]. As a result, an accumulation of inflammatory cells associated with endothelium leads to a procoagulant state [2—4]. During the first wave of the pandemic, clinicians first rapidly reported a particularly high incidence of acute pulmonary thromboembolism (APE) in COVID-19 patients [1,5] and the French Society of Vascular Medicine has provided several proposal for prevention of venous thromboembolic disease [6]. A few weeks later, reports regarding arterial thromboembolic complications have multiplied worldwide [7]. Arterial thromboembolic events in COVID-19 patients can affect the carotid and coronary arteries, as well as the renovisceral branches and peripheral arteries, therefore resulting in various clinical presentations [8]. When the aorta is involved, clinical consequences can be even more dramatic, especially in cases of acute aortic thrombosis (AAT). Depending on the aortic level, a wide range of ischemic syndromes (lower limbs, renal, mesenteric, splenic and spinal cord ischaemia) can occur, being either the revealing symptoms of COVID-19 or adding to a potential severe acute respiratory syndrome in intensive care unit (ICU) patients [9]. Regardless of COVID-19, AAT carries high morbimortality and major amputation rates [10]. When combined with COVID-19, diagnosis, treatment modalities and prognosis of AAT remain poorly described although management of AAT may be specific in this particular context. The aim of this study was to investigate specific features and clinical outcomes of AAT in COVID-19 patients.

Methods

Study population

Consecutive COVID-19 patients presenting with AAT in a tertiary referral center for acute aortic syndromes (SOS Aorta) between April 2020 and August 2021 were included in this observational retrospective cohort study. Demographic, clinical, biological and radiological data, as well as treatment modalities and outcomes were collected by means of a prospective electronic database used by the hospital. AAT included both partial and complete thrombosis of the aorta, from the ascending aorta to the aortic bifurcation and extending downstream. Patients with acute thrombosis of aortic prosthetic graft or endograft and COVID-19 negative patients with AAT were not included. Patients who were diagnosed with a chronic aortic occlusion prior to COVID-19 infection and patients with aortic dissection were not included.

Diagnosis of COVID-19 was assessed by a positive PCR test. All patients initially underwent thoracic computed tomography to estimate the pulmonary damage. In addition, a computed tomography angiogram (CTA) was performed in cases of clinical worsening or suspicion of acute limb ischaemia. Diagnosis of AAT was confirmed by CTA, as well as the initial extent of AAT and its thromboembolic complications (renal, mesenteric, splenic and lower limb).

Duplex ultrasound was not performed preoperatively in the emergency context. Ethical approval was waived for this retrospective study. The patients provided their written informed consent to participate in this study.

Medical Therapy

All patients were admitted to the ICU and were treated with intravenous unfractionated heparin (UFH) or Low-Molecular-Weight-Heparin (LMWH), associated with antiplatelet therapy (aspirin 75 mg daily) during the perioperative period. Intravenous heparin was introduced as soon as the diagnosis of acute lower limb ischemia was suspected.

Biological data (platelet, fibrinogen, D-dimer, prothrombin time) have been collected at the time of the AAT.

Indications for surgical treatment

In addition to medical therapy, surgical interventions were indicated in the urgent setting in cases of severe acute lower limb ischemia or mesenteric ischemia. The technique of revascularization was based on clinical symptoms and CTA findings (thromboembolic locations). Asymptomatic AAT were treated by conservative therapy. In cases of acute lower limb ischemia, various open and/or endovascular techniques were used such as thromboaspiration, thromboembolectomy using Fogarty catheters from the groin and/or infrapopliteal approach or bypass. Fasciotomies were eventually performed according to the severity of lower limb ischemia. In patients with acute mesenteric ischemia, thrombo embolectomy of the superior mesenteric artery was performed through laparotomy with bowel resection in case of intestinal necrosis. Thrombi were sent to virology and pathology laboratories.

Postoperative management and Follow-up

Patients were considered for early reinterventions in case of persistent or recurrence of thromboembolic events after the index procedure. Postoperatively, all patients were treated with curative doses of UFH or LMWH, associated with antiplatelet therapy. Before discharge, oral anticoagulation was introduced using vitamin K antagonist or orally active anti-Xa agent. Patients were transferred to a cardiovascular rehabilitation unit when they had undergone a major amputation or a long hospital stay. Clinical follow up was performed at three months, six months and one year. At three months, control CTA or duplex ultrasound was performed to assess patency of the target of revascularization. Oral anticoagulation was continued for six months at least.

Table 1 Clinical characteristics of the patients.

Characteristics	Patients: 10 (100%)
Age > 65 years	5 (50)
Male	9 (90)
Coexisting medical condition	
Hypertension	7 (70)
Diabetes mellitus	5 (50)
Coronary artery disease	2 (20)
Congestive heart failure	0 (0)
Dyslipidemia	7 (70)
Atrial fibrillation	3 (30)
Cerebrovascular accident	3 (30)
Chronic obstructive pulmonary disease	1 (10)
Current smoker	2 (20)
Pre-operative renal failure	0 (0)
PAD (peripheral artery disease)	2 (20)
Overweight BMI > 25 kg/m2	5 (50)
Vaccinated Covid19	0 (0)

Values are presented as mean and number (percentage)

Statistical Analysis

Discrete variables are presented as number and percentage and continuous variables as median and interquartile ranges.

Results

Patients

Ten patients (median age, 62,5 years [61—69]; male, $n = 9$, 90%) were included. Demographic data are reported in Table 1. All patients had at least one cardiovascular risk factor. Two patients had a medical history of peripheral artery disease, one of whom underwent bilateral iliac stenting in 2013. Previous medication included antiplatelet therapy ($n = 6$) and oral anticoagulation ($n = 2$). None of the patients was vaccinated against covid-19 disease. At the time of diagnosis of AAT, four patients were in ICU with orotracheal intubation. All of them were initially hospitalised for pneumopathy related to COVID-19. At the end, all AAT patients had an ICU stay. Nine patients (90%) had a symptomatic AAT: acute lower limb ischemia ($n = 9$), renal infarction ($n = 3$), mesenteric ischemia ($n = 2$) (Fig. 1), splenic infarction ($n = 2$). One patient had an asymptomatic AAT. No patient had paraplegia or stroke.

Biological findings

At admission, the median platelet count was 327 [IQR 278—397] G/L. One patient had thrombocytopenia at 115 G/L. Median fibrinogen and D-Dimer values were 5.1 [IQR 4.1—8] g/L and 4541 [IQR 3862—21913] ng/mL, respectively. The median levels of prothrombin time (PT) and activated partial thromboplastin time (APTT) were 78 [IQR 58—86] % and 1.05 [IQR 0.94—1.57], respectively. The median fibrin monomer value (data available in four patients) was 28,5 [IQR 7—71] ng/mL.

CTA findings

The median time between COVID-19 diagnosis and AAT was 5 days [IQR 0—8.5]. Thrombus localization was either the thoracic aorta ($n = 2$), the abdominal aorta ($n = 5$) or both the thoracic and abdominal aorta ($n = 3$). AAT was responsible for partial ($n = 9$) or complete ($n = 1$) occlusion. Four patients had at least one renal or visceral artery involvement, 5 patients had thromboembolic lesions in the lower limbs (Fig. 2), and 3 patients had both renal/visceral and lower limb branches extension. The detailed CTA findings are described in Table 2.

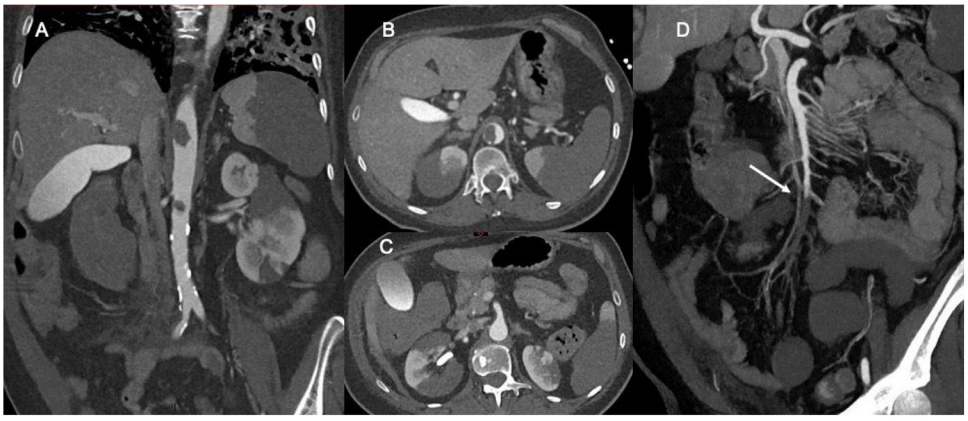

Figure 1 A 57-year-old woman who was admitted in intensive care unit for acute respiratory distress was diagnosed with AAT because of abdominal pain. Computed tomography angiogram showed multiple aortic thrombus localization in the abdominal aorta, with associated renal and splenic infarction (panel A, B & C). Panel D shows thrombus localization into the distal superior mesenteric artery (arrow) responsible for acute mesenteric ischaemia. She underwent emergent thrombolectomy of the superior mesenteric artery associated with segmental intestinal resection and temporary stoma. No revascularization of the renal arteries was attempted because of diagnosis delay > 24 hours.

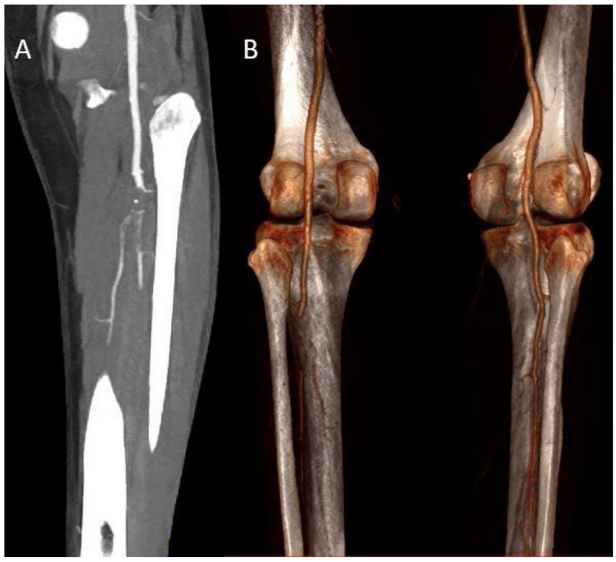

Figure 2 Postoperatively, the same patient presented with acute left lower limb ischemia. Computed tomography angiogram (panel A) revealed a popliteal thrombus extending into the tibial and fibular arteries. Panel B shows preoperative 3D reconstructions with posterior view. Revascularization was performed by percutaneous thrombus aspiration.

Table 2 Radiological findings in acute aortic occlusion covid-19 induce patients.

Radiological finding	Patients 10 (100%)
Level of aortic occlusion	
Ascending thoracic aorta	1 (10)
Arch aortic	2 (20)
Descending thoracic aorta	5 (50)
Suprarenal abdominal aorta	7 (70)
Infrarenal aorta (between the renal artery and the IMA)	3 (30)
Level of combined iliac artery occlusion	
Bilateral common iliac arteries	5 (50)
Unilateral external iliac artery	3 (30)
Bilateral external iliac arteries	2 (20)
Unilateral internal iliac artery	0 (0)
Bilateral internal iliac arteries	3 (30)
Combined common femoral artery occlusion	
Bilateral	1 (10)
Unilateral	4 (40)
Combined infra-inguinal arterial occlusion	
Unilateral FPA	2 (20)
Bilateral FPA	7 (70)
Combined visceral infarction	
Renal infarction	4 (40)
Splenic infarction	2 (20)
Superior mesenteric artery	2 (20)
Inferior mesenteric artery	1 (10)

Values are presented as number (percentage); IMA: inferior mesenteric artery; FPA: femoropopliteal artery

Medical treatment

Treatment for the pulmonary COVID-19 disease included corticoids ($n = 8$), associated with tocilizumab in three patients. Patients were initially treated with preventive anticoagulation at admission (subcutaneous LMWH, 4000UI per day - or 6000UI in case of BMI > 30 kg/m2). As soon as AAT was suspected, anticoagulation was switched to curative doses (UFH, $n = 8$; LMWH, $n = 2$). One patient with asymptomatic AAT was medically treated only with vitamin K antagonist during three months.

Surgical revascularization

Nine patients underwent revascularization interventions. The median time between diagnosis of COVID-19 and surgery was 7 days [IQR 6—13]. The median number of procedures per patient was 1 [IQR 1—2,5]. The following surgical techniques were used: thromboembolectomy ($n = 6$), thromboembolectomy thromboaspiration ($n = 2$), thromboembolectomy and in situ thrombolysis ($n = 2$). Thromboembolectomy was performed via a bilateral femoral approach ($n = 6$) or unilateral popliteal approach ($n = 2$). In one case AAT was associated with an abdominal aortic aneurysm and was therefore treated by an aortobifemoral bypass associated with a femoropopliteal thromboembolectomy. Fasciotomies were performed in 6 cases, including bilateral fasciotomies in 4. Acute mesenteric ischemia was treated by embolectomy of the mesenteric superior artery associated with intestinal resection and temporary stomia in one patient, and medically in the other patient with a favourable course. Renal and splenic infarction did not require any interventions.

Early outcomes

The 30-day mortality was 30% ($n = 3$). Postoperative deaths occurred on day 0, day 1 and day 3, respectively and were related to respiratory failure. Median ICU stay was 6,5 [IQR 0,5—11,25] days. The median duration of orotracheal intubation was 0,5 [IQR 0—2] day. Three patients required temporary dialysis (those three patients died). In one patient with bilateral acute lower limb ischemia, a major amputation (transfemoral) on the right limb and a minor amputation (transmetatarsal) on the left limb were performed, after two femoropopliteal thromboembolectomy procedures. Another patient required a minor amputation (transmetatarsal). Overall, three amputations were performed in two patients who finally survived, resulting in a free-amputation survival rate of 50%. Reinterventions were performed in three patients (redo thromboembolectomy, $n = 2$; amputation, $n = 2$; restoration of bowel continuity, $n = 1$).

Pathology analysis of thrombi

The thrombi were platelet-rich ($n = 10$), contained desquamated endothelial cells, cruoric fibrinoid material ($n = 10$), or intra-plaque haemorrhage ($n = 4$). The COVID-19 RT-PCR testing performed on the thrombi was negative in all cases

(*n* = 10). Direct bacteriology and culture remain negative findings (*n* = 10).

Follow-up

In survivors, the mean follow-up time was 3,5 [IQR 2—4.1] months. All patients underwent a control CT scan or duplex ultrasound at three months. There was no recurrence of thrombosis. The UFH or the LMWH was switched for an oral anticoagulation, antivitamin K treatment (*n* = 4), Rivaroxaban (*n* = 2), or Fondaparinux (*n* = 1) for at least three months. In the only case of asymptomatic AAT medically treated, AAT completely disappeared after three months of antivitamin K treatment. No late death was recorded during follow-up.

Discussion

We herein report a single centre retrospective cohort of ten patients with a COVID-19-related AAT at the time of the two first waves of the pandemic, before the widespread use of COVID-19 vaccines in France. Consequences of AAT were dramatic with a 30-day mortality rate of 30%, a free-amputation survival rate of 50% and a temporary stoma in one patient.

Although less common than venous thrombosis and pulmonary embolism ranging from 21.1% in inpatients [11] and up to 27% in ICU patients [12], the incidence of arterial thrombosis in COVID-19 patients is high, 3.9% in a meta-analysis pooling more than 64,000 patients [13]. The aorta and the arteries of the limbs are the privileged involved sites [14]. Moreover, these patients with arterial events have an increased mortality rate reaching up to 46% [15]. COVID-19-associated coagulopathy is revealed by early elevated fibrinogen and D-dimer levels [16] and as reported in a systematic review, elevated D-dimer levels have been associated with an increased risk of mortality [17]. COVID-19's hypercoagulability may be explained by inflammation with endothelial dysfunction [18,19] as disseminated intravascular coagulation was diagnosed in COVID-19 ICU patient with pulmonary thromboembolism and deep venous thrombosis [8]. This coagulopathy leads to thrombo-inflammatory complications and seems directly correlated with severity and poor prognosis [20].

Regarding arterial thrombosis, an underlying atherosclerosis seems to favour the presence of cruoric fibrinoid thrombi attached to an eroded atherosclerotic plaque, with platelet and intra plaque haemorrhage. This phenomenon was highlighted in a case report by Goudot et al. [21]. Demographics of our cohort (90% men, with at least one cardiovascular risk factor) support the following observation: COVID-19 patients with a high cardiovascular risk are more prone to arterial thrombosis than those with a low cardiovascular risk. Woehl et al. also reported four cases of AAT in four men with high cardiovascular risk [22]. Nevertheless, in our series pathology analysis showed no specific thrombi.

Among arterial thrombotic events, AAT might be the most severe as it involves multiple ischemic syndrome such as stroke, lower limb, renal, splenic and/or mesenteric ischemia [23]. Most reported cases of AAT were revealed by severe acute limb ischemia. Despite early anticoagulation and surgical revascularization, lower limb ischemia in these patients may be associated with major amputation, due to a high rate of early rethrombosis [24]. In case of multiple associated arterial involvement (aortic to mesenteric, renal, or lower limb thrombosis) the appropriate sequence of treatment can be tricky to determine. In our series, although thrombectomy was successful in eight out of nine cases, the risk of re-thrombosis was 10%. One patient had a transfemoral amputation after re thrombosis following femoro popliteal thrombectomy and had to undergo a transfemoral amputation following the second treatment of thromboembolectomy.

Finally, in case of incomplete AAT, the choice between aortic thrombectomy and curative anticoagulant treatment alone could be discussed in asymptomatic patients. A selective thrombectomy of thrombosed branches could represent a less aggressive approach.

Acute mesenteric ischemia is a particularly rare and dramatic complication of AAT, especially underdiagnosed in intubated-patients. Mortality in COVID-19 patients with acute mesenteric ischemia and radiological evidence of mesenteric thrombotic occlusion was 38.7% and 40%, respectively, in a review of 31 patients [25]. Mesenteric involvement thrombosis occurred in three patients in our series. Among them, only one was symptomatic and was treated by mesenteric thrombectomy associated with limited intestinal resection. This patient had a temporary stoma during three months.

Conclusion

AAT is a devastating complication of COVID-19 infection and patients with cardiovascular risk factors represent a population at high risk of arterial thrombo-embolic events. AAT had dramatic consequences in terms of mortality and amputation rates. Early diagnosis and surgical repair are paramount to limit poor outcomes. Hopefully widespread use of vaccines might eventually reduce the risk of COVID-19 related AAT in the future.

Disclosure of interest

The authors declare that they have no competing interest.

Human and animal rights

The authors declare that the work described has not involved experimentation on humans or animals.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

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Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

CRediT authorship contribution statement

- C. Caudron, I. Ben Abdallah, S. El Batti: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Validation, Visualization, Writing— original draft and review & editing.

- P. Julia, J.M. Alsac, T. Mirault, G. Detriche, R. Cherkaoui: Conceptualisation, Investigation, Methodology, Validation, Writing — review & editing.

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