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ACUTE LIMB ISCHEMIA IN CRITICALLY ILL COVID-19 PATIENTS: A CASE SERIES AND LITERATURE REVIEW

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ABSTRACT

Background: The vascular burden increased by COVID-19 infection and including acute limb ischemia (ALI) quickly emerged as a major medical challenge with devastating consequences such as limb loss, multiorgan dysfunction and death. We report a case series of COVID-19 infection associated with ALI to raise awareness and knowledge towards this life-threatening association.
Methods: COVIDS-19 patients with acute limb ischemia (ALI) managed in a Moroccan 14 beds COVID-19 ICU between March 2020 and January 2021, were reviewed. Data collected included demographics, clinical presentation, treatments and outcomes.
Results: Over the 10-month period, our ICU cared for 407 hospitalized patients with confirmed COVID-19. A total of 6 COVID-19 patients with ALI were identified. The mean age was 61 years (52 - 70) and 5 were men. The most common preexisting condition was diabetes (50%). The mean CRP level was 219 mg/L. Five patients had thrombus in multiple locations. No concomitant deep vein thrombosis was identified. Four patients presented with signs of acute arterial ischemia with or without respiratory symptoms and were subsequently diagnosed with COVID-19. The remaining two patients developed ischemia during hospitalization. Mean SOFA score was 5 (2 - 9). Respiratory support, corticosteroids and heparin therapies were used in all patients. Intubation and vasopressors were required in four patients. Revascularization was performed in five patients and reintervention was necessary in three cases. Four patients died in the ICU while two were successfully discharged.
Conclusion: ALI in COVID-19 patients is a challenging life-threatening vascular emergency that requires appropriate multidisciplinary management (intensivists, anesthesiologists, vascular surgeons and interventionists, radiologists, haematologists…) and further studies focused on anticoagulation.
Keywords: Acute Limb ischemia; coagulopathy; SARS-CoV-2; Thrombosis.

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INTRODUCTION

Coronavirus Disease (COVID-19) is no longer considered an infectious lung disease with a traditional ARDS (Acute Respiratory Distress Syndrome) but rather a convergence of vascular dysfunction, thrombosis, and dysregulated inflammation, that can lead to multi-organ failure and death [**1, 2**]. COVID-19 induced hypercoagulability is linked to a significant increasing risk of arterial and venous thrombosis [**3, 4**]. The vascular burden increased by COVID-19 infection and including acute limb ischemia (ALI) quickly emerged as a major medical challenge with devastating consequences such as limb loss, premature intubation, multiorgan dysfunction and death [**5**]. Bellosta et al reported an increasing incidence of ALI during the pandemic peak (16.3% versus a baseline rate of 1.8% in the region study) and poorer surgical results due to the associated acquired hypercoagulability [**6**]. We report a case series of COVID-19 infection associated with ALI since awareness and knowledge of this life-threatening association may improve early clinical identification and appropriate management.

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METHODS

This is a single center retrospective study conducted in a Moroccan 14 beds COVID-19 ICU over the period from March 24, 2020 to January 1st, 2021. All patients infected with COVID-19 and presenting acute limb ischemia (ALI) were included. The diagnosis of COVID-19 was based on real-time polymerase chain reaction (rt-PCR) of nasopharyngeal swab or serological blood test and/or chest CT scan. ALI was assessed by the vascular surgery team of our tertiary university hospital. Data collected included demographics, co-morbidities, clinical presentation, treatments and outcomes.

RESULTS

Throughout the 10-month study period, our unit cared for **407** hospitalized patients with confirmed COVID-19 infection. A total of **6** COVID-19 patients with ALI were identified. The mean age was 61 years (range 52 - 70) and 5 were men. Four of our patients had co morbidities and were at risk of atherosclerosis while the other two were active with no co morbidities. The most common preexisting condition was diabetes (50%). Four patients presented with signs of acute arterial ischemia with few or no respiratory symptoms and were subsequently diagnosed with COVID-19. The two remaining patients developed limb ischemia within 2 and 5 days following hospitalization. The mean CRP level was 219 mg/L. Computed tomography angiogram was diagnostic in five patients while one patient was too unstable for transport to imaging. The diagnosis in this latter case was based on clinical signs of acute ischemia. The lower extremity was affected in all our patients and thrombosis of large (aorta, iliac) and medium-sized (superficial/deep femoral, popliteal) arteries were the most commonly found. Four patients had multi-located arterial thrombi and no coexisting deep vein thrombosis was detected. Mean SOFA score was 5 (Range 2 -9). Respiratory support, corticosteroids and heparin therapies were used in all patients. Intubation and vasopressors were required in four patients. One patient was deemed too unstable for surgical intervention. Revascularization surgeries were performed in five patients under general or regional anesthesia as required by the patients and re-intervention was necessary in three cases. Out of the five operated patients, three received open thrombectomy, one received open thrombectomy over two interventions and one bypass surgery, and one received endovascular thrombectomy, open thrombectomy, bypass surgery and secondary amputation over four interventions. Four patients died in the ICU while two were successfully discharged. **Table I** summarizes characteristics, diagnosis, management and outcomes of our patients.

Table I: Summary of patient characteristics, diagnosis, management and outcomes in our case series.

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (year old), gender	70, male	63, female	56, male	60, male	52, male	69, male
Co-morbidities	0	Hypertension Diabetes Coronary disease Hyperthyroidism	Diabetes	0	Diabetes Active smoking Intermittent claudication	Active smoking Intermittent claudication
Charlson Comorbidity Index	3	4	2	3	4	3
Usual antithrombotic therapy	No	Aspirin 75mg/day Curative anticoagulation	No	No	No	No
Antithrombotic therapy at time of arterial event	Curative anticoagulation	Curative anticoagulation	No	No	No	No
Symptoms on hospital admission	Respiratory	Respiratory	Respiratory + Acute right lumb ischemia	Respiratory + Lumb Ischemia	Lumb Ischemia	Respiratory+ Lumb Ischemia

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COVID-19 infection						
Time to hospital consultation (days)	7	10	8	3	NA	2
Clinical presentation	Severe ARDS	Severe ARDS	Severe ARDS	Severe ARDS	NA	ARDS
RT-PCR	Negative	Negative	Positive	Positive	Positive	Positive
IgG Serology	Positive	Positive	NA	NA	Positive	NA
Chest CT scan	Damage > 55%	Damage 75%	Damage > 75%	Damage ≥75%	Bacterial-type condensation + No PE	Damage 25 -50%
Arterial ischemia event						
Days COVID onset to thrombotic event	11	12	8	4	Unknown	0
Symptoms	Right leg acute ischemia	Left leg acute ischemia	Acute bilateral lumb ischemia	Acute left lumb ischemia	Acute right lumb ischemia	Acute bilateral lumb ischemia
CT angiography	NA	**Descending thoracic aorta:** Unstable ulcerated atheroma plaque **Left**: popliteal + internal iliac arteries occlusion **Right:** deep femoral artery occlusion	Bilateral primitive iliac arteries subtotal stenosis **Left:** Tibio-peroneal trunk total stenosis **Right:** internal iliac artery subtotal stenosis + popliteal artery and tibio-peroneal trunk total stenosis	Total occlusion of the left popliteal artery	Occlusion of the right primitive iliac and popliteal arteries	**Sub-renal aorta:** atheroma **Superior mesenteric artery:** Subtotal occlusion **Left :** primitive iliac and common femoral arteries occlusion **Right**: common femoral artery occlusion
Treatment	Medical	Medical + embolectomy	Medical + embolectomy	Medical + embolectomy/ Bypass	Medical + embolectomy/ Bypass/ Amputation	Medical + embolectomy
Complication	-	No	No	Reocclusion	Reocclusion	Hematoma
Number of Interventions	0	1	1	3	4	2
Anesthesia	-	Spinal	Spinal	General	General	General
Concomitant deep vein thrombosis	No	No	No	No	No	No

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Severity assessment						
Shock	Yes	No	No	Yes	Yes	Yes
Respiratory failure	Yes	Yes	Yes	Yes	Yes	Yes
SOFA	7	2	4	4	9	8
Lee Criteria*	3/6	2/6	1/6	1/6	2/6	1/6
Blood parameters						
Creatinine, mg/l (Range 8 - 14,40)	9	8	10	6	22	25
WBC, /mm3	20450	12035	14800	14400	6630	23840
C-reactive protein, mg/l (NR 0 – 5)	256	115	200	242	319	183
CPK, IU/l (NR 0 - 171)	63	877	429	451	2396	4803
LDH, IU/l (NR 0 - 248)	-	-	649	432	400	3325
Platelets, /mm^3	435000	583000	270000	400000	56000	193000
Prothrombin Time / INR	83.5% /1.06	81.6% / 1.13	68% / 1.16	78% / 1.11	60% / 1.24	83% / 1.08
D-dimer ng/mL (NR 0 – 500)	-	-	900	3430	2880	-
Ferritin µg/l (NR 20 -300)	-	829	950	-	983	1164
Troponin, ng/ml (NR 0.00 - 0.08)	-	0.025	0	0.007	0.018	0.016
Organ support therapies	Intubation Vasopressors	High flow oxygen therapy	HFNC, NIV, Prone	Intubation Vasopressors	Intubation Vasopressors	Intubation Vasopressors
ICU stay (days)	5	13	14	13	19	11
Outcome	Death Cardiogenic shock	Hospital discharge 7 days after ICU discharge	Hospital discharge 48 hours after ICU discharge	Death MOF	Death MOF	Death MOF

ARDS: Acute Respiratory Distress Syndrom $PaO_2/FiO_2 \leq 300$; MOF: Multiple Organ Failure; NA: Not Applicable; NR: Normal Range; PE: Pulmonary Embolism; RT-PCR: Real Time Polymerase chain reaction; SOFA: Sequential Organ Failure Assessment; WBC: White Blood Cell Count. *Lee criteria: High risk surgery; coronary artery disease; congestive heart failure; cerebrovascular disease; diabetes mellitus on insulin; serum creatinine>2mg/D

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DISCUSSION

Despite anticoagulation, a high number of critically ill COVID-19 patients developed life-threatening thrombotic complications [3, 4], which raised questions about the unique physiopathology of COVID-19. Findings suggest that COVID-19 may predispose to both venous and arterial thromboembolism due to excessive inflammation, cytokine release, endothelial dysfunction, immobilization, hypoxia, and diffuse intravascular coagulation [2]. As a consequence of the COVID-19 induced coagulopathy, ALI emerged as a new crisis during the current pandemic as cases were constantly reported worldwide, and even among non-atherosclerotic COVID-19 patients [6 - 21]. As data result from case series and case reports, the incidence is not well studied and widely variable ranging from 0.3% [22] to 16.3% [6]. In the Italian observational study, Bellosta and al concluded that COVID-19 infection might increase the incidence of ALI (16.3% during the pandemic peak versus a baseline rate of 1.8% in the region study) and be associated with poorer surgical results due to the induced hypercoagulability [6]. The incidence may be higher among critically ill patients as they are highly hypoxemic and inflammatory and because of immobilization. Within 10 months and among the 407 COVID-19 patients admitted to our unit, we provided care for six COVID-19 patients with acute limb ischemia. ALI typically occurs in hospitalized patients with severe COVID-19 within five to seven days after respiratory decompensation but can also affects patients with mild COVID-19 ALI [6, 22 - 24]. Moreover, it can be the sole clinical manifestation of COVID-19 [25, 26] as in the case of our patient 5 (**Table I**) or occur following recovery [27, 28]. ALI can develop in COVID-19 patients with no usual risk factors such as older age, obesity, and cardiovascular co morbidities and even when receiving thromboprophylaxis [6, 22 - 24]. The thrombosis of large and medium size vessels of the lower extremity [6, 22 - 24] is more commonly reported than the upper limb [29 -31] while thrombosis of small vessels can be related to vasopressors administration [32]. Thrombosis of prior vascular reconstruction involving stents and bypass grafts have also been reported [33]. Our findings are consistent with the reported clinical features above. COVID-19 induced hypercoagulability is likely related to an inflammatory cascade that leads to an endothelial thrombo- inflammatory syndrome through cytokine storm, complement activation, and endotheliitis. The virus itself may possibly activate the coagulation cascade through its receptors (angiotensin-converting enzyme 2) on vascular muscle and endothelial cells membrans [2, 34]. Increasing D-dimer and inflammatory biomarkers such as C-reactive protein, leukocytes, ferritin, lactate dehydrogenase and interleukin-6 in hospitalized patients may thus indicate the occurrence of thrombotic events [35 -37]. The severity of ALI determines the urgency and type of diagnostic evaluation and course of treatment. This vascular emergency is associated with significant morbidity and mortality and is defined as < 2 weeks of severe hypoperfusion of the limb characterized by new or worsening symptoms featuring the 6 Ps: pain, pallor, poikilothermia, pulselessness, paresthesia and paralysis. The diagnosis is predominantly clinical and vascular imaging (duplex ultrasound, computed tomographic angiography) confirms the location and extent of arterial obstruction [38]. Therefore, imaging should be guided by resources availability and patient stability and should not delay therapeutic management, especially in hypoxemic COVID-19 patients whose transport can be a real challenge. Since timely and appropriate therapeutic anticoagulation is crucial when it comes to limb salvage and overall survival [6], all our patients received bolus followed by continuous infusion of intravenous unfractionated heparin (UFH). It is suggested that heparin efficacy is related to both its anticoagulant and anti-inflammatory properties of inhibiting several chemokines and complement and its antiviral properties of reducing viral binding through its action on the virus' spike protein [39]. However, heparin efficiency may be impaired by a number of coagulation abnormalities observed in COVID-19 patients, such as heparin resistance [40, 41] or heparin-induced thrombocytopenia. The difficulty to achieve the target activated cephalin time (ACT) when treating with UFH have been observed in our patients and thrombotic events requiring re interventions occurred in two cases despite apparently adequate anticoagulation on biology. In this highly inflammatory context, the assessment of ACT or aPTT may be not reliable since it may not reflect the real anti-Xa activity. Intervention decision in COVID-19 patients is conditioned by the severity of systemic illness. Similar to damage control in trauma patients, the principle of "life over limb" is justified. Because of the virus-induced hypercoagulability and despite revascularization attempts (endovascular, open surgical), poorer surgical results and higher mortality and limb loss rates are observed in severe COVID-19 patients with ALI [5, 6, 42]. Following intervention, all our patients were maintained on therapeutic anticoagulation and an antiplatelet agent (Asprin) to reduce incidence of recurrent ischemic events. Out of the five operated patients, two required re-intervention because of a recurrent thrombotic occlusion within the first 48 hours. Bellosta et al have concluded that prolonged

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systemic heparin might improve surgical treatment efficacy, limb salvage, and overall survival [6] but additional data on anticoagulation management for COVID-19 related ALI are needed and even anticipated [43]. In our case series, prognosis was generally poor and seems largely driven by both the overall physiologic condition at presentation and the impact of COVID-19 which induced coagulopathy severity. Non survivals had higher SOFA score and required more organ support and reinterventions. Among COVID-19 patients who develop ALI, mortality rates are as high as 50% and may be higher among ICU patients [5, 6, 23, 24]. Several studies have reported that D-dimer levels were significantly associated with poor prognosis [37, 44, 45]. While each facility has developed guidelines and protocols for prophylactic and therapeutic anticoagulation, based or not on D-dimer levels, optimal management is still evolving rapidly as we continually acquire new insights into the disease physiopathology. ICU COVID-19 patients being at higher thromboembolic risk, our local consensus includes both a therapeutic dose of anticoagulation and anti-aggregation in the absence of obvious contraindications. The risk of hemorrhage seems no significant compared to the thrombotic risk but further anticoagulation focused studies with detailed hematological monitoring are needed to avoid a one-size-fits-all anticoagulation management. Lastly, this study has several limitations due to its retrospective and monocentric nature but adds to the previous accumulating data while raising awareness towards the poor prognosis of COVID-19 thrombosis and the challenge facing clinicians while managing this condition.

CONCLUSION

Arterial thromboembolic complications carry devastating consequences of limb loss, multiorgan dysfunction and death. ALI in COVID-19 patients is a challenging life-threatening vascular emergency that requires appropriate multidisciplinary management (intensivists, anesthesiologists, vascular surgeons and interventionists, radiologists, haematologists…) and further studies focused on anticoagulation.

CONFLICT OF INTEREST:

None.

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