Case Report

Successful Systemic Heparinization for Treatment of Acute Arterial Occlusion of Tibial Artery and Aortic Mural Thrombi in a Patient With COVID-19 Infection: A Case Report

Nawaphan Taengsakul MD[1]

[1] Department of Surgery, Chulabhorn Hospital, HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, Bangkok, Thailand

The present case report described a 60-year-old woman who developed multiple isolated acute arterial occlusions of the left anterior tibial artery, peroneal artery, and posterior tibial artery with aortic mural thrombi in the infrarenal aorta during treatment of COVID-19 pneumonia. The patient underwent conservative treatment by systemic heparinization and switched to low molecular weight heparin. She experienced clinical improvement within hours of medical treatment and complete resolution of the tibial artery thrombosis after two weeks of treatment. The aortic mural thrombi was evaluated by computed tomography angiography (CTA) abdomen and lower extremities and resolved after six weeks of anticoagulant administration.

Keywords: Acute limb ischemia; Aortic mural thrombi; Thrombosis; COVID-19

Received 20 September 2021 | Revised 5 April 2022 | Accepted 20 April 2022

J Med Assoc Thai 2022;105(5):472-9

Website: http://www.jmatonline.com

Patients with coronavirus disease 2019 (COVID-19) commonly develop pulmonary and cardiovascular complications[1]. Research has demonstrated that patients with COVID-19 infection are in a hypercoagulable state, which increased risk of arterial and venous thrombosis[1]. A meta-analysis of 1,083 COVID-19 patients showed the prevalence of thrombosis was 22% and increased to 43% after admission to the intensive care unit (ICU)[2]. Patients with thrombosis had a substantial risk to death[3]. Klok et al[3] analyzed 184 patients with COVID-19 in the ICU and found the incidence of thrombosis was 31% with venous thromboembolism in 27% and acute limb ischemia (ALI) in 3.7%.

ALI is an emergency condition in patients with vascular disease caused by a sudden decrease in arterial limbs perfusion. The incidence of ALI has significantly increased during the COVID-19 pandemic, and the rate of successful revascularization is lower than expected[4] with high rates of amputation and mortality[5]. Other reports have described aortic mural thrombi in patients with COVID-19 who developed embolic complications[4-7]. Silingardi et al[4] suggested that an important part of the preoperative workup in patients with COVID-19 who developed ALI should be thoraco-abdominal computed tomography angiography (CTA). The present report described a case of ALI with aortic mural thrombi in a patient with COVID-19 pneumonia. The patient provided written informed consent for reporting the details and images related to her illness.

Correspondence to:

Taengsakul N.

Department of Surgery, Chulabhorn Hospital, HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, 906 Kamphaeng Phet 6 Road, Talat Bang khen, Lak Si, Bangkok 10210, Thailand.

Phone: +66-2-576-6791, **Fax**: +66-2-576-6791

Email: nawaphan.tan@cra.ac.th

How to cite this article:

Taengsakul N. Successful Systemic Heparinization for Treatment of Acute Arterial Occlusion of Tibial Artery and Aortic Mural Thrombi in a Patient With COVID-19 Infection: A Case Report. J Med Assoc Thai 2022;105:472-9.

DOI: 10.35755/jmedassocthai.2022.05.13302

Case Report

A 60-year-old woman presented with left lower limb pain that had started six hours prior to arrival at the hospital. She felt the pain on the plantar side of left foot. She had been diagnosed with COVID-19 pneumonia 12 days earlier, confirmed by a swab test and chest CT. She had been treated with favipiravir and dexamethasone for 10 days. Her medical history included type 2 diabetes with no history of atrial fibrillation or arrhythmia. Her body temperature was 36.5°C, pulse rate was 66 beats per minute, regular rhythm, respiratory rate was 20 breathes per minute,

Table 1. Laboratory results on admission

	Result	Reference value
Complete blood count		
Hemoglobin (g/dL)	12.4	11 to 14.7
Hematocrit (%)	37.8	35.2 to 46.7
MCV (fL)	73	87.1 to 102.4
MCH (pg)	23.9	26.8 to 32.4
MCHC (g/dL)	32.8	19.6 to 32.5
White blood cell (/uL)	14,230	3,170 to 8,400
Platelet count (/uL)	362,000	167,000 to 390,000
Neutrophil (%)	90.7	39.7 to 71.2
Lymphocyte (%)	5.8	21.9 to 50.3
Monocyte (%)	3.0	4.2 to 9.6
Eosinophil (%)	0.1	0.6 to 4.9
Chemistry		
BUN (mg/dL)	20	6 to 20
Creatinine (mg/dL)	0.77	0.51 to 0.95
eGFR (mL/minute/1.73 m^2)	84.2	>60
Sodium (mmol/L)	137	136 to 145
Potassium (mmol/L)	4.4	3.5 to 5.1
Chloride (mmol/L)	100	98 to 107
CO_2 (mmol/L)	27	22 to 29
CRP (mg/L)	3.94	<5
ESR (mm/hour)	45	<20
Lactate (mmol/L)	2.1	0.5 to 1.6
Glucose (mg/dL)	147	70 to 110
Coagulation test		
Prothrombin time (seconds)	11.4	9.3 to 12.3
INR	1.00	
aPTT (seconds)	18.7	20.9 to 30.1
aPTT ratio	0.76	
Fibrinogen (mg/dL)	457.5	165 to 400
Thrombin time (seconds)	152.40	12 to 16
D-dimer (ng/mL)	3,627	<500
CPK (U/L)	45	<170
Hypercoagulable state workup		
Anticardiolipin IgM (U/mL)	<2	<12
Anticardiolipin IgG (U/mL)	<2	<12
Beta 2 Glycoprotein IgG (U/mL)	<2	<20
Beta 2 Glycoprotein IgM (U/mL)	<2	<20
Protein C (%)	172.8	70 to 140
Protein S (%)	51.1	54.7 to 123.7
Lupus anticoagulant aRVVT (seconds)	38.00	29.8 to 47.3
Homocystein (μmol/L)	8.00	<15
Antithrombin activity (%)	126.2	83 to 128

MCV=mean corpuscular volume; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; CO_2=carbon dioxide; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; INR=international normalized ratio; aPTT=activated partial thromboplastin time; CPK=creatine phosphokinase; aRVVT=dilute Russell's viper venom time

blood pressure was 135/75 mmHg, and oxygen saturation was 95%. Physical examination revealed her left foot was mildly swollen and cold on palpation. The plantar side was tender but showed no weakness. There were no signs of intrinsic muscle weakness or skin mottling. Loss of proprioception sensation was found at the toe level of the left foot. The left femoral pulse and popliteal artery were present, while the dorsalis pedis artery and posterior tibial artery were absent on palpation and Doppler examination. Doppler examination of the venous system showed normal findings. The respiratory system was stable with no tachypnea. The Cardiovascular examination showed a regular rhythm with no murmur.

Laboratory tests showed a high D-dimer concentration, normal coagulation, and normal results of a hypercoagulable state workup (Table 1). The COVID-19 RNA was still detectable. An echocardiogram revealed normal findings.

Acute arterial occlusion of the left anterior tibial artery, peroneal artery, and posterior tibial artery (Rutherford's class IIA) was initially diagnosed, and CTA showed intraluminal thrombus involving the left proximal of peroneal artery, proximal of posterior tibial artery and distal of anterior tibial artery. Reconstitution of flow was seen at the distal peroneal artery. A focal concentric filling defect was presented within the infrarenal abdominal aorta at the L2 level (Figure 1). There was no evidence of aortic arteriosclerosis and only minimal arteriosclerosis of the lower extremity arteries.

The patient underwent standard dose heparin infusion with a target activated partial thromboplastin time ratio of 1.5 to 2.5. The author decided to refer the patient because the author's hospital was a primary service and the patient had universal coverage at another hospital. The destinate hospital accepted the referral case; however, requiring time for admission and referral management due to limited resources.

Two hours after initiation of intravenous heparin, the patient experienced dramatic resolution for her pain, and her skin became warm. However, the pulses of dorsalis pedis artery and posterior tibial artery were still absent on palpation and Doppler examination.

Eight hours after initiation of systemic heparinization, pain was absent, and the skin was normal in color. The pulses of dorsalis pedis artery and posterior tibial artery were still absent on palpation and Doppler examination. The destinate hospital informed the present case hospital that they could not receive the patient because of facility limitations.

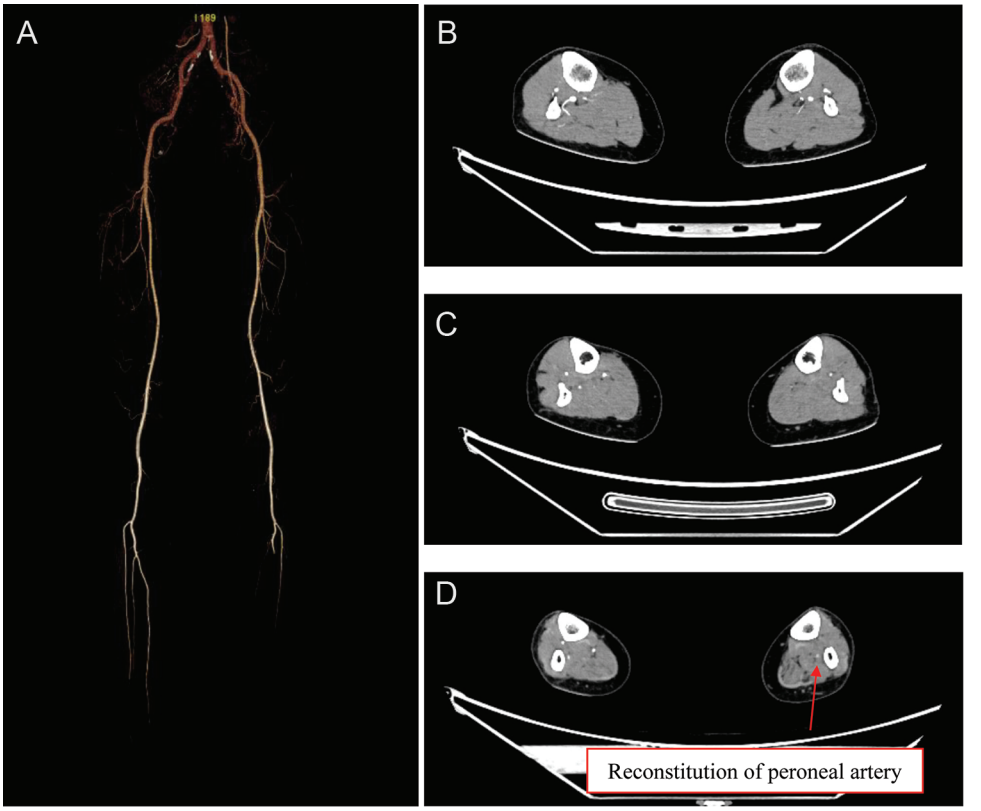

Figure 1. Three-dimensional reconstruction of computed tomography arteriography (CTA) demonstrated the arterial occlusion of the left anterior tibial artery, peroneal artery, and posterior tibial artery (A). Axial views of CTA showed contrast medium passed to the proximal posterior tibial artery, peroneal artery, and anterior tibial artery (B). (C) An abrupt change of the posterior tibial artery and peroneal artery, and contrast medium passed to the proximal posterior tibial artery and peroneal artery; however, contrast filling was still present at the anterior tibial artery. Reconstitution of the peroneal artery with occlusion of the distal anterior tibial artery was observed (D).

The author decided to perform conservative treatment by systemic heparinization in the isolation unit of the emergency room and admitted the patient to the COVID ward when a bed became available. Intravenous heparin was continued for three days and switched to low molecular weight heparin (LMWH) on day four. A chest radiograph was sent for follow up evaluation of COVID-19 pneumonia. It revealed infiltration of both lungs and increased consolidation of the left lower lung compared to the previous imaging (Figure 2). The infectious specialist decided to continue the favipiravir and dexamethasone. After admission (on day 2), the patient could perform normal activity and reported no pain. Her respiratory system was stable.

On day five, CTA revealed partial resolution of the filling defect at the peroneal artery, a small size with contrast filling defect at the posterior tibial artery, and complete recanalization of the anterior tibial artery (Figure 3). The patient was discharged on day six after anticoagulant administration and continued a therapeutic dose of LMWH. The patient was scheduled for repeat CTA two weeks after anticoagulant administration and found complete recanalization of the anterior tibial artery, posterior tibial artery, and peroneal artery. CTA revealed a decrease size of concentric intraluminal thrombus of the infrarenal abdominal aorta (Figure 4). CTA at six weeks revealed complete resolution of the intraluminal thrombus (Figure 5). The patient was planned to continue the anticoagulant therapy for at least three months. Summarized imaging finding of tibial lesions is in Table 2.

Discussion

COVID-19 is a novel disease with a very broad spectrum involving different organ systems caused by a hypercoagulable state. The pathophysiology of COVID-19 induced thrombosis is complex. The agent that causes COVID-19 is a single-stranded RNA

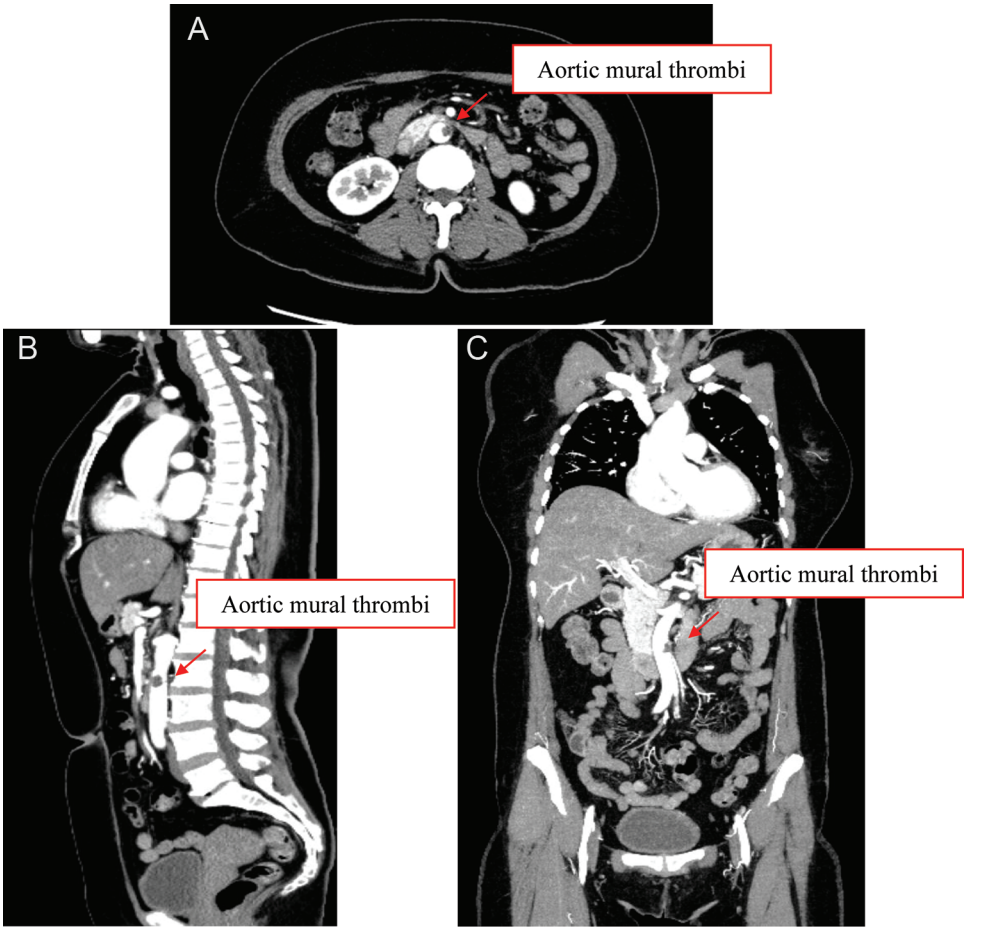

Figure 2. Computed tomography arteriography (CTA) demonstrated floating aortic mural thrombi at the infrarenal abdominal aorta in the (A) axial view, (B) coronal view, and (C) sagittal view.

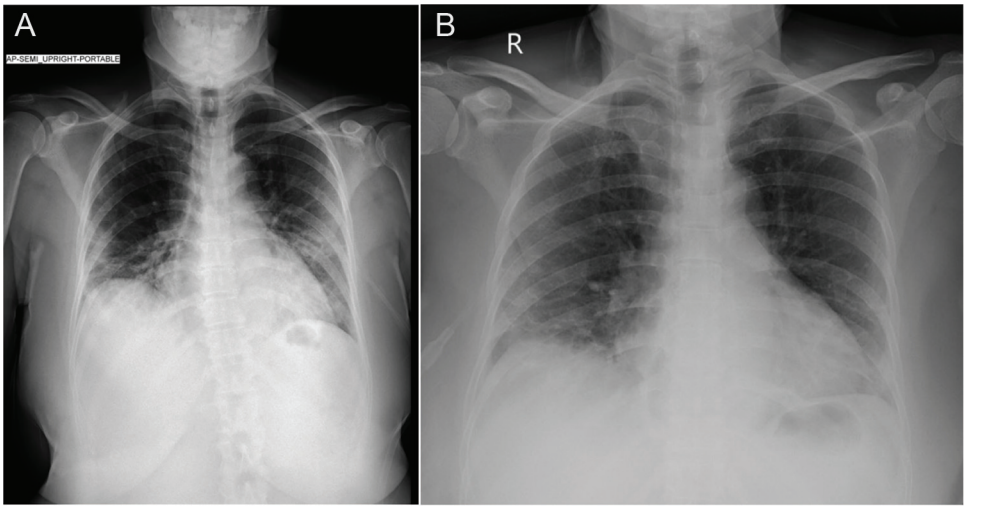

Figure 3. (A) Chest radiogragh at admission compared with (B) chest radiogragh5 days before admission.

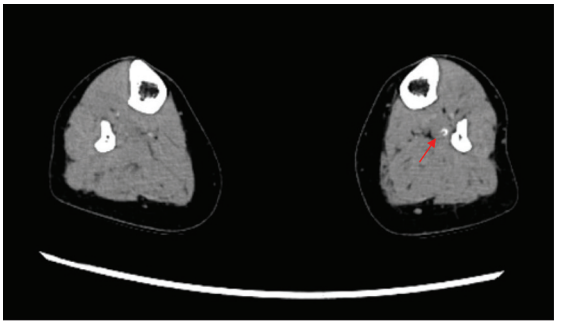

Figure 4. Computed tomography angiography (CTA) on day 5 after anticoagulant administration showed partial resolution of the filling defect at the peroneal artery (arrow).

virus that acts on the vascular endothelium via the angiotensin-converting enzyme-2 receptor and induces an intense immune response known as the cytokine storm. The cytokine storm precipitates systemic inflammatory response syndrome (SIRS) causing systemic macrothrombosis and microthrombosis[1].

The pathophysiology underlying how COVID-19 induces ALI is not well understood, but theories have been proposed. Emerging evidence suggests that COVID-19 is associated with endotheliitis from direct viral invasion, historically characterized by diffuse endothelial damage in areas infiltrated by inflammatory cells[8]. COVID-19 is associated with

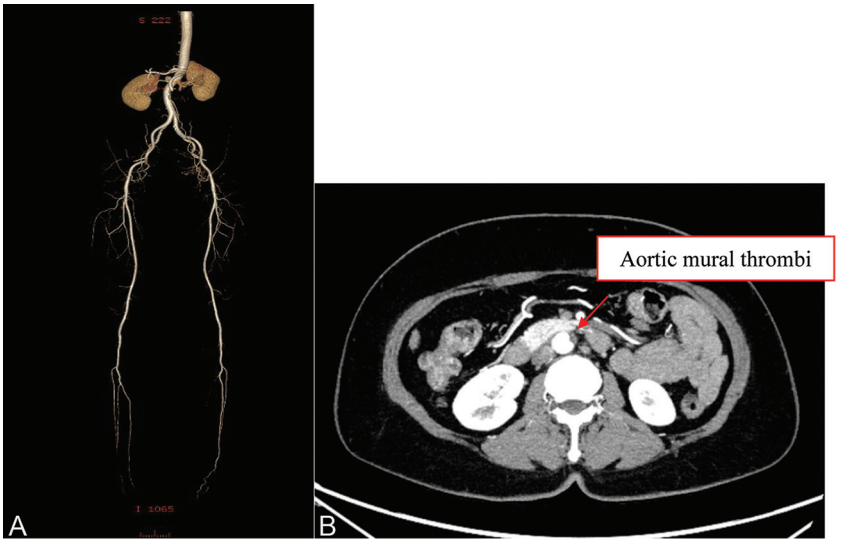

Figure 5. Computed tomography angiography (CTA) on day 14 after anticoagulant administration showed (A) complete recanalization of the anterior tibial artery, posterior tibial artery, and peroneal artery on three-dimensional reconstruction, with (B) a decrease in the size of the concentric intraluminal thrombus of the infrarenal abdominal aorta in the axial view.

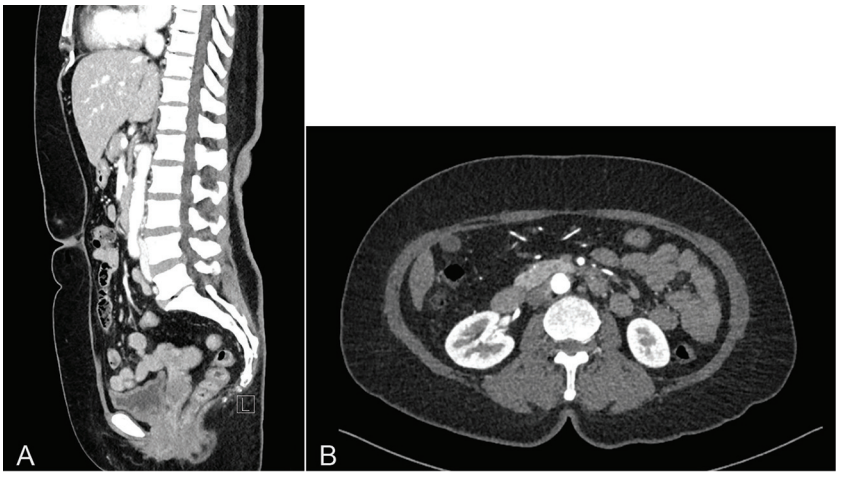

Figure 6. Computed tomography angiography (CTA) on day 45 after anticoagulant administration showed complete resolution of the intraluminal thrombus on the (A) sagittal view and (B) axial view.

Table 2. Comparison of tibial lesions from admission day to 45 days after treatment

Location of tibial arteries	CTA findings		
	Day 1	Day 5	Day 14
Anterior tibial artery	Absent flow at distal artery	Absent flow at distal artery	Complete resolution
Posterior tibial artery	Absent flow at proximal artery	Absent flow at distal artery	Complete resolution
Peroneal artery	Absent flow at proximal artery and reconstitution at distal artery	Partial resolution of filling defect	Complete resolution

CTA=computed tomography angiography

a hypercoagulable state with elevation of D-dimers, prothrombin, and fibrinogen concentration[9]. In the present case, the patient had an elevated D-dimer and fibrinogen concentration. However, there was no available evidence on how long inflammatory and thrombotic derangement would last after recovery from COVID-19 symptoms.

The clinical presentation of ALI is unpredictable and unrelated to the severity of the disease and the viral load. Patients presented with Rutherford class IIA and IIB ischemia with Rutherford IIA in 28% to 77% of and Rutherford IIB in 17% to 75%[10]. The correlation between the timing of COVID-19 and ALI is not clear. Reports have described ALI as the first presentation of COVID-19. However, many hospitalized patients will develop ALI during hospitalization, and the onset varies from 6.6 to 15.77 days after admission for COVID-19 symptoms[10]. Arterial thrombosis typically occurs in the lower extremities. The most common location of lower extremity ALI is the femoropopliteal region (64.7%), followed by the tibial arteries (29.4%), and "desert foot" as neither the dorsalis pedis artery nor plantar artery 23.5%[10].

The management of ALI varies according to the symptoms and overall severity of the disease. If an intervention is needed, methods may be chosen including conventional embolectomy, catheter directed thrombolysis, and mechanical thrombectomy. The main surgical modality is conventional embolectomy[10]. Primary amputation may be performed in patients with non-salvageable limb ischemia[10]. A meta-analysis of 199 patients from 34 studies showed that the mean age of the patients was 61.6 years with a range of 39 to 84 years, and medical treatment was selected as the first line treatment for 41.8% of the patients. Medical treatment was associated with a higher risk of death than any intervention[11]. A previous report indicated that resource limitations and admission of critically ill patients with infection were associated with high volumes of medical treatment and high mortality rates[11]. However, Tang et al[12] showed that anticoagulant treatment with LMWH was associated with a lower mortality risk in patients with a high D-dimer concentration. Furthermore, there is high evidence of successful medical treatment. Topcu et al[13] reported a case of tibial artery thrombosis for which embolectomy was unsuccessful but in which clinical improvement was achieved after intravenous heparin and iloprost infusion. Surya and Santoso[14] described a patient with COVID-19 who developed acute thrombosis of the superficial femoral artery. The patients recovered after therapeutic dosing of LMWH on an outpatient basis. Veerasuri et al[15] reported a case of bilateral ALI with oral anticoagulant treatment. The patient had thrombosis of the right superficial artery and left popliteal artery. The symptoms were relieved after treatment with rivaroxaban.

Aortic mural thrombi had been found in patients with COVID-19 who developed embolic complication[4-7]. Silingardi et al[4] suggested that an important part of the preoperative workup for ALI in patients with COVID-19 is thoraco-abdominal CTA. The pathophysiology of aortic mural thrombi formation involves is direct viral invasion of endothelial cells via the angiotensin-converting enzyme 2 receptor, resulting in endothelial injury and free-floating aortic thrombi[10]. The risk factors for aortic mural thrombi are concomitant cardiovascular disease, older age such as older than 60 years, moderate to severe pneumonia, and significantly increased inflammatory markers[16,17]. There are reports of aortic mural thrombi in patients with COVID-19, and most were managed conservatively. Borrelli et al[5] reported two cases of aortic floating thrombi that completely resolved after anticoagulant treatment.

The patient described in the present report presented with sudden onset of limb pain after 10 days of treatment of COVID-19 pneumonia. A chest radiograph showed active infection due to progression of consolidation. The patient had acute arterial occlusions of the left tibial arteries with aortic mural thrombi at the infrarenal aorta. The cause of the acute arterial occlusion in the present patient

was inconclusive. The causes were thrombosis of the native artery or small emboli from aortic mural thrombi, causing acute arterial occlusion of unknown pathology. The severity of ischemia was designated Rutherford class IIA. The clinical presentation showed loss of sensation at the toe level with no intrinsic muscle weakness, and the pulse examination revealed absent arterial Doppler signal of all tibial arteries with presence of a venous Doppler signal. The patient was treated conservatively because of rapid recovery after anticoagulant administration and limited resources. The patient was initially treated with intravenous heparin, which was switched to a therapeutic dose of LMWH. At day 14 of anticoagulant therapy, CTA revealed complete resolution of the tibial arteries and a significantly decrease in the size of aortic mural thrombi. At day 45 of anticoagulant therapy, the complete resolution of the aortic mural thrombi was observed. There is no strong recommendation on how long anticoagulant therapy should be continued for patients with ALI. The present patient was able to dexterously injected LMWH by herself and had financial limitations preventing treatment with a direct-acting oral anticoagulant. Therefore, the LMWH was planned to be continued for at least three months as the primary treatment and discontinued if the D-dimer concentration returned to a normal level. The main limitation of the present case report is the inconclusive pathophysiology of the patient's condition.

For patients with COVID-19 presenting with ALI, the choice of intervention may be limited by the number of available beds, exposure to stressful procedure, the need to limit exposure of medical personnel, and the need to conserve resources. The present case report revealed successful of conservative treatment in a patient with multiple isolated acute arterial occlusions of tibial arteries with Rutherford class IIA ischemia. The author believes that these finding will be beneficial for the treatment of ALI during the COVID-19 pandemic.

Conclusion

A conservative approach with anticoagulants may be appropriate in selected case. Patients with COVID-19 who exhibited with multiple isolated acute arterial occlusions of tibial arteries with Rutherford class IIA ischemia can undergo medical treatment as definitive treatment. Treatment of the aortic mural thrombi with an anticoagulant in the present patient with COVID-19 was the conservative first-choice approach.

What is already known on this topic?

Conservative treatment with anticoagulant therapy was an alternative treatment of ALI in patient with COVID-19. Anticoagulant for treatment of aortic mural thrombi might be an acceptable option.

What this study adds?

Anticoagulant therapy for ALI in patients with COVID-19 might be used for limb salvageable in patients with Rutherford classification IIA.

Acknowledgement

The author acknowledges Angela Morben, DVM, ELS, from Edanz (www.edanz.com/ac), for editing a draft of this manuscript.

Conflicts of interest

The author declares no conflict of interest.

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