CASE SERIES

EXTRA-PULMONARY THROMBOSIS IN PATIENTS WITH CORONAVIRUS-19 DISEASE; CASE SERIES AND REVIEW OF THE LITERATURE

Madiha Iqbal, Sher Muhammad Sethi, Sadaf Hanif
Aga Khan University Hospital, Karachi-Pakistan

Background: Coronavirus disease 19 (COVID-19) is a viral disease caused by SARS-CoV-2. There is an increased incidence of a thromboembolic phenomenon in patients with COVID-19 infection. Pulmonary embolism is the most common thrombotic presentation in COVID-19 patients. Extra-pulmonary thrombosis is an unusual thrombotic complication of COVID-19 disease. **Methods:** This study was conducted at The Aga Khan University Hospital from June-July'2021. Patients clinical and laboratory findings, treatment, and outcomes were recorded. **Results:** We report three cases with the diagnosis of COVID-19 pneumonia associated with extra-pulmonary thrombosis from June to July 2021. The mean age of the patients were 66.3 and two of them (66.6%) were male. The diagnosis of COVID-19 was confirmed by real-time reverse transcriptase-polymerase chain reaction analysis in all the three patients. Extra-pulmonary thrombosis was identified in the celiac artery and splenic veins in case 1, left common iliac artery in case 2, and left ventricular apical thrombus in case 3. All the patients were treated with anticoagulation. In total, two patients were discharged home after total recovery, while the third patient died. **Conclusion:** The take-home message is that COVID-19 infection is a pro-thrombotic condition that can provoke arterial and venous thrombosis. Extra-pulmonary thrombosis is increasingly identified with COVID-19 infection. It is important to remember that the patient might have no potential risk factor for thromboses, as COVID-19 infection per se is a risk to induce thrombosis.

Keywords: COVID-19; Thrombosis; Venous and arterial thrombosis; Intracardiac thrombus; Therapeutic anticoagulation

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INTRODUCTION

Coronavirus disease 19 (COVID-19) is a viral disease caused by SARS-CoV-2. The first outbreak occurred in December 2019 in Wuhan, China, and quickly become a global pandemic.[1] The clinical spectrum of this disease varies from flu-like infection to severe pneumonia and acute respiratory distress syndrome.[2] With time, COVID-19 disease is associated with a hypercoagulable state. There is an increased incidence of a thromboembolic phenomenon in patients with COVID-19 infection.[3] Pulmonary embolism is the most common thrombotic presentation in COVID-19 patients.[4] Extra-pulmonary thrombosis is an unusual thrombotic complication of COVID-19 disease. Here, we report three different cases of extra-pulmonary thrombosis in patients with COVID-19 disease.

MATERIAL AND METHODS

We included three patients with COVID-19 admitted at The Aga Khan University Hospital (AKUH), Karachi, Pakistan from June'2021 to July'2021 were included in the study. The AKUH is a 650 bed, JCIA certified, tertiary care university hospital, which was the first hospital in the country to admit COVID-19 patients.

Patients were included on basis of laboratory confirmed diagnosis of COVID-19 based on their positive reverse transcriptase-polymerase chain reaction (RT-PCR) assay and evidence of thrombosis which was confirmed by the different radiological modalities.

Chest radiology consisted of a standard anteroposterior view. Computed tomography (CT) of abdomen was reviewed whenever available. Ultrasound Doppler and magnetic resonance imaging of head was also reviewed were applicable. All radiological images were reviewed by a senior consultant radiologist, with greater than 10 years' experience along with their fellow/resident. Echocardiography was also included which was done by trained echocardiographic technician and reported by a senior cardiologist.

Ethical review committee of the institute reviewed the study proposal and cases and was exempted with reference number 2021-6359-17979.

A *proforma* was filled that includes patients clinical and laboratory findings, treatment, and outcomes. Investigator filled the proforma and was re-evaluated by the senior consultant. SPSS Version 23 was used for data analysis. Categorical variables were summarized, as counts and percentages. Descriptive statistics was used to summarize the data, and the results were shown in mean and standard deviation

RESULTS

We report three cases with the diagnosis of COVID-19 pneumonia associated with extra-pulmonary thrombosis from June to July 2021. Two of the patients were managed in high dependency units/special care units (HDU/SCU) while one patient was intubated and managed in intensive care unit (ICU). The mean age of the patients were 66.3 and two of them (66.6%) were male. All the patients had cough prior to admission. Hypertension was present in two (66.6%) patients. Demographics and clinical characteristics are shown in detail in table-1.

On an initial investigation, one patient had a low white cell count ($0.3x10^9$ per µL). Biochemical markers were unremarkable. Ferritin and LDH was elevated in two of the patients. Table-2 shows the laboratory parameters of the patients at the time of admission. The chest x-ray on the day of admission showed extensive peripheral opacification in bilateral lung field in the first patient while the others were insignificant as shown in Figure-1. The diagnosis of COVID-19 was confirmed by real-time reverse transcriptase-polymerase chain reaction analysis in all the three patients. Supplemental oxygen and non-invasive ventilation (i.e., continuous positive airway pressure (CPAP) or bi-level positive airway pressure (bi-PAP)) was used by all the patients. One patient was unable to tolerate non-invasive ventilation and was intubated and kept on an invasive ventilator. Patient 1 had persistent hypoxia and abdominal pain. Computed tomography of the chest and abdomen was done which showed diffuse bilateral areas of ground-glass opacification in bilateral lung field, filling defect noted in the aorta at the origin extending up to the celiac trunk, similarly filling defect was noted in the splenic vein causing splenic infarcts (Figure-2 and 3). Patient 2 had left leg pain and colour doppler scan of left limb suggested atherosclerotic changes in the left common iliac artery, with no flow in anterior tibial, posterior tibial, and dorsalis pedis artery (Figure-4).

Patient 3 had a low Glasgow coma scale score on presentation (8/15) so underwent an emergent computed tomography of the brain showed acute ischemic stroke involving the left posterior cerebral artery territory (Figure-5). For work-up of stroke, transthoracic echocardiography was done that showed an ejection fraction of 25% with global hypokinesia and a left ventricular apical thrombus, aortic and mitral valves were normal (Figure-6).

ANA was negative in all the patients. Lupus antibodies were negative in one patient. Intravenous steroids and remdesivir was given to all the patients. Extra-pulmonary thrombosis was managed with anticoagulation. One patient stay was complicated by pneumomediastinum and pneumothorax, upper gastrointestinal bleed, and superimposed bacterial and fungal infection. He continues to worsen clinically and passed away from these complications. Management and outcomes are summarized in table-3.

Table-1: Demographics and clinical characteristics of the patients

Characteristics	Patients (N = 3)	%
Age in years (mean ± S.D)	66.3 ± 15.5	
Gender		
Male	2	66.6
Female	1	33.3
Diabetes	1	33.3
Hypertension	2	66.6
Chronic Kidney Disease	1	33.3
Clinical Features (On admission):		
Fever	2	66.6
Cough	3	100
Dyspnea	2	66.6
Vitals (on admission): mean ± S.D.		
O2 Saturation	86.3 ± 10.0	%
Respiratory rate	29 ± 5.5	breath/min
Heart rate	99.3 ± 14.2	beats/min
Systolic blood pressure	156.6 ± 30.5	mmHg
Diastolic blood pressure	93.3 ± 5.7	mmHg

Table-2: Laboratory parameters of all the patients on the day of admission

	Range	Case 1	Case 2	Case 3
Haemoglobin (g/dL)	11-14.5	13.8	14.4	12.8
White cells (x 10^9 per µL)	4-10	7.7	6.8	0.3
Platelets (x 10^9 per µL)	154-433	245	174	309
Activated partial thromboplastin time (s)	22-34	27.4	27.7	26.3
International normalized ratio	0.9-1.2	1.1	1.1	1.3
Sodium (mmol/L)	136-145	128	137	145
Potassium (mmol/L)	3.5-5.1	4.2	5.0	3.2
Creatinine (mg/dl)	0.6-1	1.1	3.4	1.3
Aspartate Aminotransferase (U/L)	<35	22	31	44
Alanine Aminotransferase (U/L)	<35	104	122	56
Bilirubin (mg/dL)	1.0	0.1-2	0.3	1.4
D-dimer (mg/L)	0.7	<0.5	NA	>30
C-reactive Protein (mg/dL)	0-14	133	NA	NA
LDH (mg/dL)	120-240	789	NA	698
Ferritin (ng/ml)	10-291	1885	NA	1337

LDH: lactate dehydrogenase; NA: not available

Table-3: Management and outcomes

	N (%)
Steroids	3 (100%)
Remdesivir	3 (100%)
Tocilizumab	2 (66.6%)
Anticoagulation: 1. Enoxaparin 2. Unfractionated heparin	 2 (66.6%) 1 (33.3%)
Mortality	1 (33.3%)
Length of hospital stay (in days) Mean ± Standard deviation	 6.6 ± 1.5

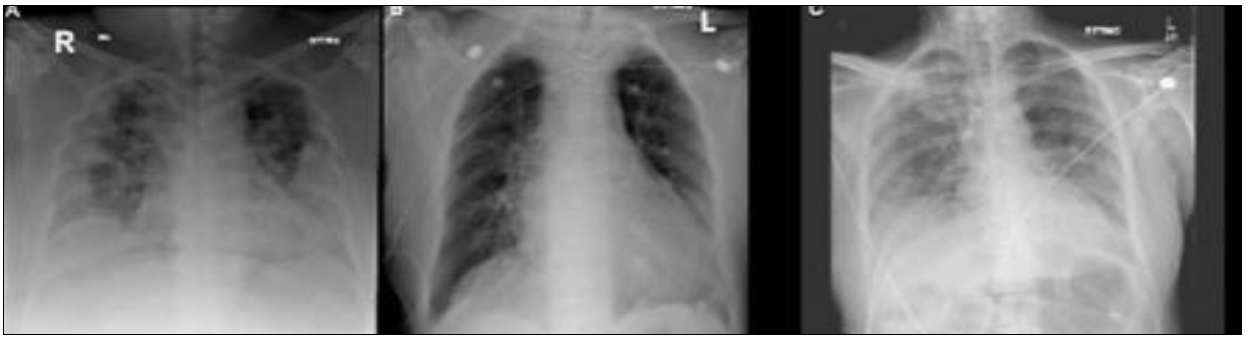

Figure-1: Chest x-ray of the patients 1 (A), of the patient 2 (B), and of the patient 3 (C)

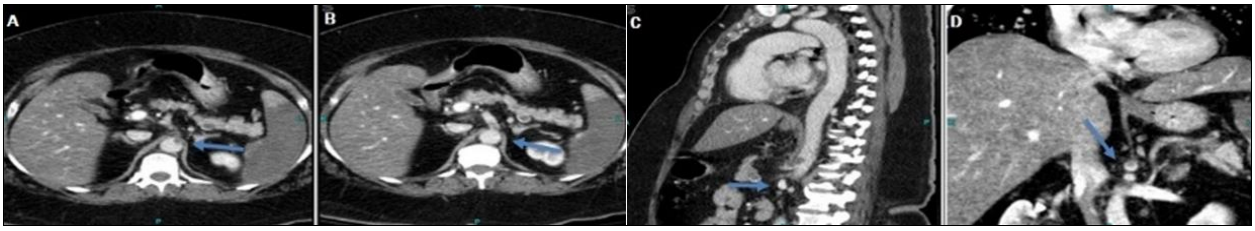

Figure-2: CT scan of the abdomen showing filling defect in the origin of celiac axis extending in the celiac trunk (celiac artery thrombosis) shown with blue arrow in A, B, C and D

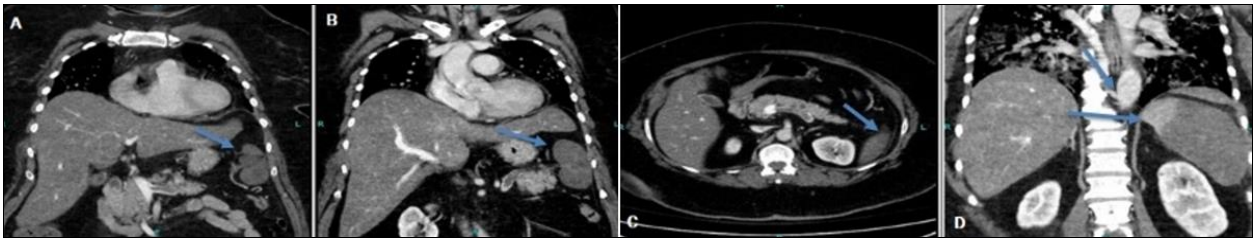

Figure-3: CT scan of the abdomen showing filling defect in the splenic veins (A, B) which is causing splenic infarcts (C, D)

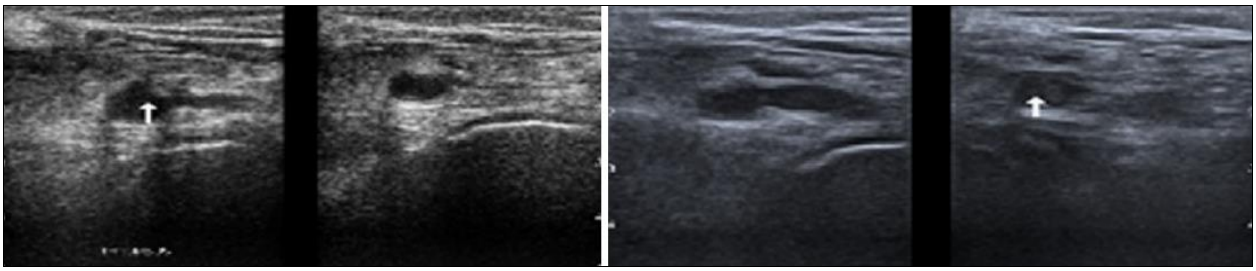

Figure-4: Atherosclerotic changes in the common iliac artery, with no flow in anterior and posterior tibial artery and dorsal pedis artery on doppler ultrasound

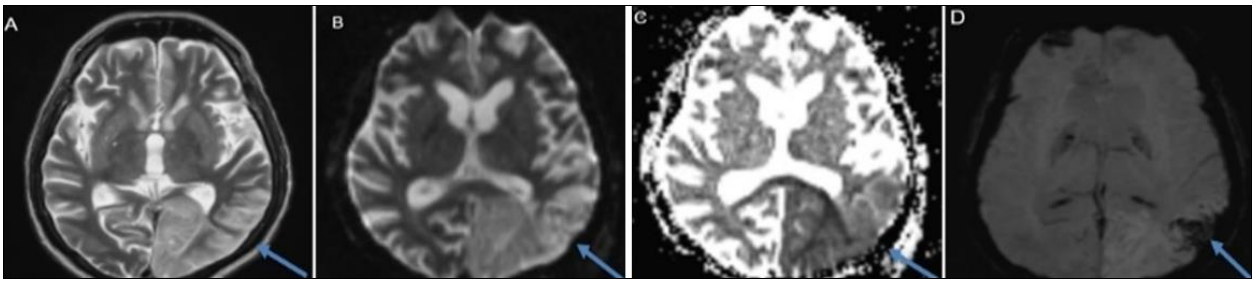

Figure-5: Different views of head MRI demonstrates acute middle and posterior cerebral artery stroke, axial T2 (A), axial DWI (B), axial ADC (C), and axial SWI (D)

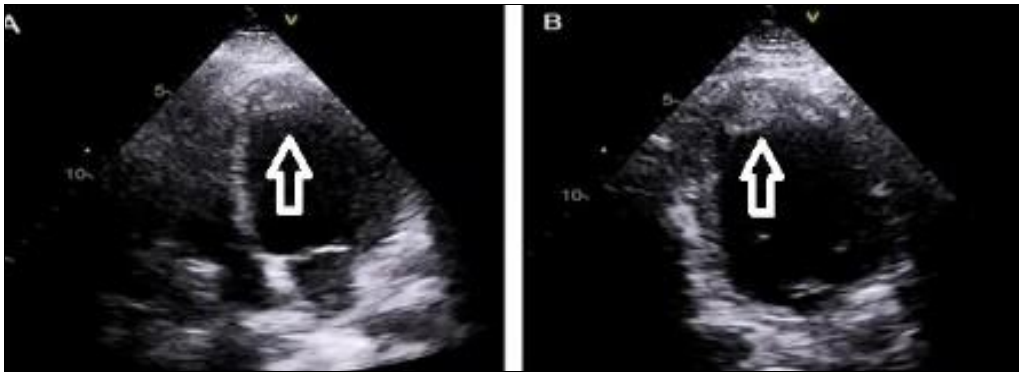

Figure-6: Echocardiography showing left ventricular apical thrombus shown by white arrow

DISCUSSION

We report in this case series cases of extra-pulmonary thrombosis at three different locations of the body in patients with COVID-19 disease. Surprisingly, all three patients had extra-pulmonary thrombosis at the initial presentation to the hospital with their COVID-19 infection.

SARS-CoV-2 has a potential tendency to facilitate hypercoagulability by a cross-linkage mechanism between thrombosis and inflammation. COVID-19 disease is a pro-inflammatory disease and is thought to cause inflammatory thrombosis.[5] Considering this, there are past studies that have documented pulmonary embolism in patients with COVID-19 disease. The incidence of pulmonary embolism is increasing exponentially in COVID-19 patients and had been associated with worse outcomes.[6,7] The prevalence of thromboembolic events with COVID-19 infection is not well known. However, thrombotic complications with COVID-19 in intensive care units have been reported around 25-31%. Most of these patients had a pulmonary embolism, deep venous thrombosis, and cerebral infarction.[8]

An extra-pulmonary thrombotic complication is a rare entity and had a great impact on COVID-19 patient's morbidity and mortality.[9] Arterial thrombosis with COVID-19 is more unique and had not been frequently reported. Here we reported three different cases of thrombosis in unusual areas of the body. In our first case, the patient started to have general symptoms of COVID-19 disease. She was in a pro-inflammatory state as evidence by high inflammatory markers on admission. Despite optimal treatment, she was hypoxic and for further evaluation, she underwent a

computed tomography scan of the chest and abdomen where she was incidentally found to have thrombosis in the celiac trunk and splenic veins. She was treated with anticoagulation and showed significant improvement and completely recovered on her follow-up visit. Mui et al. had reported celiac artery thrombosis in there one patient but she was an elderly female with diabetes and hyperlipidaemia making him prone to thrombotic complications.[10] Moreno et al. had reported a rare case of portal vein thrombosis with COVID-19 disease without any thrombotic risk factor in the patient.[11]

The second case showed an elderly male with mild respiratory symptoms presented with acute left limb pain. He had no background history of smoking and diabetes. He had chronic kidney disease which was well controlled. This sudden onset of acute limb pain was evaluated and Doppler studies confirmed the diagnosis of acute limb ischemia secondary to arterial thrombosis. Anticoagulation was the only treatment offered to this patient and showed great improvement and was up and about without any residual pain by day 5 of anticoagulation. Kashi et al. had reported five cases of critical limb ischemia with COVID-19 disease but all of them had a cardiovascular risk factor and most of them had potential complicated COVID-19 requiring intensive care treatment.[12] A similar presentation of acute limb ischemia with COVID-19 disease was also found to have lupus anticoagulants and was treated with thrombectomy and thrombolysis.[13]

In the third case, there were respiratory symptoms along with muscle weakness and loss of consciousness. He was diagnosed to have an acute stroke. Echocardiography showed a left ventricular apical thrombus. Due to persistent hypoxia, computed tomography of the chest was done which showed pulmonary embolism along with splenic and renal infarcts. Further, the course of COVID-19 was complicated with pneumomediastinum and pneumothorax. Anticoagulation was held due to an upper gastrointestinal bleed. Due to multi-organ involvement, the family opted for no escalation of therapy and the patient had a brady arrest. Imaeda *et al*. had reported a case of left ventricular thrombus with COVID-19 infection in dilated cardiomyopathy patients.[14] Another case of intra-cardiac thrombus with COVID-19 infection was managed with percutaneous thrombectomy and right ventricular mechanical support.[15]

Standard prophylactic anticoagulation in COVID-19 patients is recommended by the American College of Chest Physician. Despite this, there is a risk of thromboembolism in these patients.[16] INSPIRATION trial had recommended an intermediate dose of anticoagulation in critically ill COVID-19 patients.[17] We also managed our patients with anticoagulation and had shown good results. Early treatment can prevent the worsening of symptoms. The dosage of anticoagulation should be judicious and balance between risk and adverse side effects.

This shows that COVID-19 infection is a hypercoagulable state which can not only cause venous but also arterial thrombosis. Further large observational studies are required to estimate the prevalence of thrombotic burden of disease in COVID-19 infections. Secondly, we need to observe whether anticoagulation is the only management option in these patients. The role of steroids in preventing inflammation can also reduce the risk of thrombosis need to be evaluated. Another important aspect is the role of anti-platelets. We didn't use any anti-platelets in our patients but their importance needs to be stratified.

There are certain limitations in our cases as we don't have aggressive pro-thrombotic work-up that includes protein C and S levels, anti-thrombin III levels, and factor V leiden mutation was not excluded. Secondly, we have recently treated these patients and we need to follow the first two cases to look for long term outcomes. Further imaging will be required in future to visualize resolution of thrombosis.

CONCLUSION

The take-home message is that COVID-19 infection is a pro-thrombotic condition that can provoke arterial and venous thrombosis. Though pulmonary embolism is common, extra-pulmonary thrombosis is increasingly identified with COVID-19 infection. It is important to remember that the patient might have no potential risk factor for thromboses, as COVID-19 infection per se is a risk to induce thrombosis.

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Address for Correspondence:

Sher Muhammad Sethi, C-218, Unit-11, Block-1, Gulistan e Johar, Karachi, 75290-Pakistan
Cell: +92 313 255 1542
Email: sher.sethi@gmail.com