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Case Series

Internal Medicine Section

Multifaceted COVID-19 Associated Coagulopathy: A Case Series

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ABSTRACT

The pathophysiology behind Coronavirus Disease-2019 (COVID-19) has remained blur even after more than two years of onset of the pandemic. Apart from pulmonary parenchymal involvement, widespread vascular thrombosis affecting both pulmonary and extra-pulmonary systems has also been seen to contribute to COVID-19 associated morbidity. This vascular manifestation often remains undiagnosed due to non specific and varied symptoms that range from asymptomatic detection to life threatening presentations. A series of six COVID-19 positive (three male and three female) cases who presented with thrombosis of pulmonary, coronary and cerebral vessels despite being on thromboprophylaxis are reported herein. The age of patients ranged from 32 to 80 years. Out of six patients, three had co-morbidities. The most common complication was Pulmonary Thromboembolism (PTE, n=3) followed by Brain infarct (n=2) and Myocardial Infarction (MI, n=1). Out of three patients with PTE, one patient had concurrent Deep Vein Thrombosis (DVT). All patients were managed as per guidelines issued by the Ministry of Health and Family Welfare for severe COVID-19 disease. Out of six patients, three patients died and three were discharged. The series highlights the need for high index of suspicion on the part of the treating physician that could aid in early detection and successful management of this potentially fatal condition.

Keywords: Complications, Coronavirus disease 2019, Thrombosis

INTRODUCTION

The spectrum of COVID-19 Associated Coagulopathy (CAC) is wide and can involve both arteries and veins. Besides Deep Vein Thrombosis (DVT), it may present as life threatening conditions like Cerebrovascular Accident (CVA), MI and massive Pulmonary Thromboembolism (PTE) [1,2]. A study by Bilaloglu S et al., revealed the incidence of ischaemic stroke and MI in COVID-19 as 0.9-4.6% and 1.1-8.9%, respectively. The mortality was almost double in patients with thrombotic events (43.2%) [3]. A recent meta-analysis reported that the pooled incidence of PTE was 21% [4].

The exact pathophysiology of CAC is still not known even after more than two years of onset of the pandemic. However, several theories have been postulated. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has affinity towards Angiotensin Converting Enzyme-2 (ACE-2) receptors which are commonly present in lungs. Other sites include vascular endothelial cells, kidney, heart, and brain. Virus induced endothelial damage leads to raised levels of von Willebrand factor and activation of neutrophils and macrophages in multiple vascular beds. Cytokine release syndrome and formation of Neutrophil Extracellular Traps (NETs) are also linked to thrombotic complications in COVID-19 patients [4-6]. Commonly, elderly patients with co-morbidities who are on immunosuppressive therapy develop CAC. But infrequently, young patients may also deteriorate rapidly due to thromboembolic complications even in absence of any predisposing factors [2,3,7]. So, one should have a high index of suspicion to identify uncommon presentations irrespective of age, gender and underlying health conditions.

A series of six cases aged 32 to 80 years with COVID-19 who presented with varied thromboembolic complications reported to our institution from March-July 2021. None of the patients had any history of malignancy, long haul travel or previous immobilisation. It is pertinent to understand that CAC as an entity is not so rare and the clinician should be aware of its varied presentations. Details of patients are summarised in [Table/Fig-1].

CASE SERIES

Case 1

A 68-year-old COVID-19 positive male got admitted with complaints of Shortness of Breath (SOB), chest pain and pain in the right lower limb for the last five days. He was a known diabetic and hypertensive

Serial No./Variables	1	2	3	4	5	6
Age/Gender	68 Y/M	58 Y/F	38 Y/M	80 Y/F	32 Y/F	49 Y/M
Co-morbidities	DM HTN	HTN CAD	Nil	DM	Nil	Nil
Confirmation of COVID-19	RT-PCR	RT-PCR	RAT	RT-PCR	Clinico-radiological	Clinico-radiological
Vaccination status	Two doses	One dose	Nil	Two doses	Nil	Nil
Evidence of DVT on Venous Doppler USG	Yes (Thrombosis in right femoro-popliteal vein)	No	Not done	No	No	No
Other tests	CECT chest: Acute PTE in left lobar and right and left segmental PA. Mildly dilated left PA Cystic bronchiectasis RLL	CEMRI brain: Partial sigmoid sinus thrombosis with acute infarct bilateral frontal lobes	ECG: STEMI Anterior wall Trop I –Negative	NCCT head: Right cerebellar infarct X-ray chest: Bilateral pneumonia	CECT chest: Pulmonary thrombus involving bilateral PAs and right inferior PV with bilateral pneumonia primarily subpleural.	CECT chest: Partial thrombosis left PA anterior segmental branch with bilateral pneumonia
Prophylactic anticoagulation	Yes	Yes	Yes	Yes	Yes	Yes
Oxygen support	Nil	NRM	NRM	NRM	NRM	Invasive ventilation

Management plan	Therapeutic anticoagulation	Therapeutic anticoagulation	Thrombolysis	Therapeutic anticoagulation	Therapeutic anticoagulation	Ventilator settings as per ARDS-net protocol
Outcome	Discharged	Death	Death	Death	Discharged	Discharged

[Table/Fig-1]: Summarising details of patients' history, radiological findings, management and outcome.
Y: Age in years; M: Male; F: Female; DM: Diabetes mellitus type-2; HTN: Hypertension; CAD: Coronary artery disease; RT-PCR: Reverse transcription polymerase chain reaction; RAT: Rapid antigen test; DVT: Deep vein thrombosis; USG: Ultrasonography; CECT: Contrast enhanced computed tomography; PTE: Pulmonary thromboembolism; PA: Pulmonary arteries; RLL: Right lower lobe; CEMRI: Contrast enhanced magnetic resonance imaging; ECG: Electrocardiogram; STEMI: ST segment elevated myocardial infarction; Trop I: Troponin I; PV: Pulmonary vein; NRM: Non rebreathing mask; ARDS: Acute respiratory distress syndrome; NCCT: Non contrast computed tomography

since three years and on oral therapy (metformin 500 mg twice daily and amlodipine 10 mg once daily). Three months back, he had been successfully treated for moderate COVID-19.

On admission, his vitals were stable with percent Oxygen Saturation (SpO_2) of 96% at Room Air (RA). Chest X Ray (CXR) was normal. Venous Doppler Ultrasonography (VD-USG) revealed DVT in right femoro-popliteal veins. He was started on therapeutic anticoagulation (Low Molecular Weight Heparin; LMWH subcutaneous, SC; 0.6 mL twice daily) along with supportive treatment as per the guidelines issued by the Ministry of Health and Family Welfare [8]. On day 5, he developed sudden increase in SOB with hypoxemia (SpO_2 86% RA). Computed Tomography with Pulmonary Angiography (CTPA) showed acute PTE in left lobar and right and left segmental pulmonary arteries. He gradually improved with therapeutic anticoagulation. He was later discharged on oral rivaroxaban (20 mg once daily) for three months. He did not report for scheduled follow-up.

Case 2

A 58-year-old COVID-19 positive female, presented with complaints of fever, cough, and SOB for five days and poor food intake for two days. She was a known case of hypertension (seven years) and Coronary Artery Disease (CAD) (three years) on oral drugs; metoprolol (25 mg), aspirin (75 mg) and atorvastatin (20 mg).

On admission, she was delirious (Glasgow Coma Scale; GCS-11/15). Her vitals were: Blood Pressure (BP)- 150/100 mmHg, Pulse Rate (PR)- 120/minute, and SpO_2-80% RA. She was started on remdesivir (i.v.; 200 mg once daily on day 1 followed by 100 mg for next four days), dexamethasone (6 mg i.v. twice daily), LMWH (0.6 mL s.c. twice daily) and oxygen therapy (non rebreathing mask, NRM; FiO_2 0.80-1.0) as per the guidelines. Investigations revealed dyselectrolemia (serum Na^+- 98 mEq/L, K^+- 3 mEq/L) and right bundle branch block on Electrocardiogram (ECG). She improved with electrolyte supplementation. On day 7, she developed acute confusional state. Repeat blood investigations were normal. Magnetic Resonance Imaging (MRI) of brain was done to rule out Central Pontine Myelinolysis (CPM) which showed partial sigmoid sinus thrombosis with acute infarct involving bilateral frontal lobes. She was referred to a higher centre where she died before any intervention could be done.

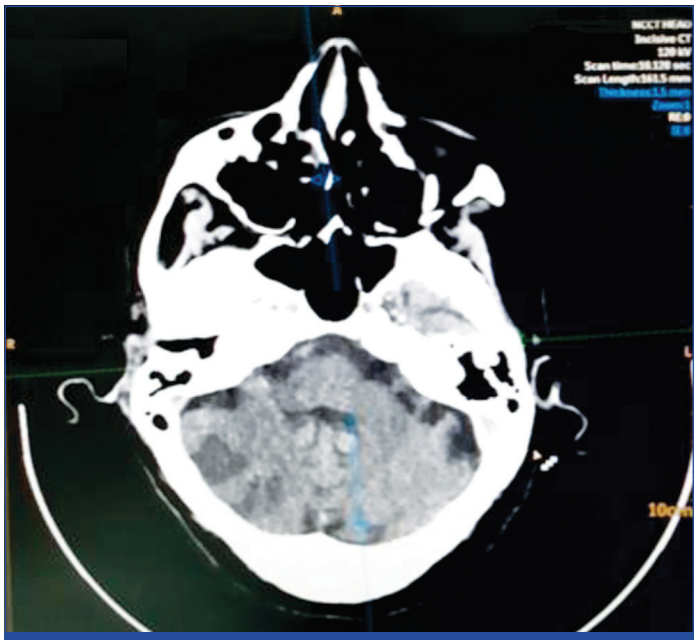
Case 3

A 38-year-old COVID-19 positive unvaccinated male with no co-morbidities presented with complaints of cough and SOB for the last five days. On examination, he was tachypneic (respiratory rate; RR-28 per minute) with SpO_2 of 75% at RA. CXR revealed bilateral peripheral patchy infiltrates. He was managed with remdesivir, dexamethasone, LMWH and oxygen therapy as per protocol.

On day 3, he complained of severe retrosternal chest pain. ECG showed findings of anterior wall ST segment elevated MI. He was immediately started on anti-platelets and clopidogrel and shifted to cardiac-care-unit for thrombolysis, however he had a fatal cardiac arrest on the same day.

Case 4

An 80-year-old COVID-19 positive female was admitted with complaints of SOB for four days. CXR revealed bilateral pneumonia. She was a diabetic and was receiving metformin (500 mg once daily) and vildagliptin (50 mg once daily) for 12 years. Her vitals were: BP-150/80 mmHg, PR- 110/minute, RR- 32/minute, and SpO_2 of 80% at RA. Blood investigations revealed Acute Kidney Injury (AKI) (serum urea- 89 mg/dL, creatinine-1.1mg/dL) with normal electrolytes, mild hepatitis (aspartate transaminase, AST; 49U/L, alanine transaminase, ALT; 88U/L), and normal total leucocyte count (TLC; 9300/µL). She was managed on lines of severe COVID-19 as per protocol. She showed some initial signs of stabilisation, however, on tenth day, she became drowsy with GCS of 10/15. Non Contrast Computed Tomography (NCCT) head revealed right ischaemic cerebellar infarct [Table/Fig-2]. Due to persistent worsening, she was put on a ventilator. However, she died after two days.



[Table/Fig-2]: NCCT head showing hypodense area in right cerebellum suggestive of infarct.
NCCT: Non contrast computed tomography

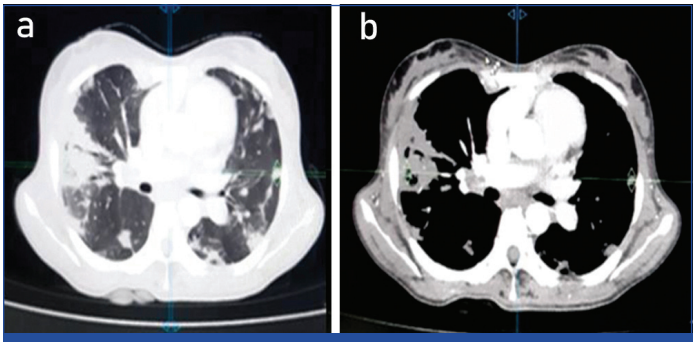
Case 5

A 32-year-old female was admitted in severe acute respiratory infection ward with chief complaints of SOB and cough since 10 days. On examination, her BP was 124/80 mmHg, PR- 99/min, RR-24/min and SpO_2 89% at RA. She had a history of recent contact with COVID-19 positive patient in her family however her Reverse Transcription-Polymerase Chain Reaction (RT-PCR) report for SARS-CoV-2 came out negative. CXR was suggestive of bilateral pneumonia. COVID-19 Reporting And Data System (CORADS) score on High Resolution CT (HRCT) of the thorax was 5 out of 6.

She was extensively evaluated to rule out alternative causes. Her serology for H1N1 influenza, dengue, leptospira, and scrub typhus was negative. Sputum for Acid Fast Bacilli (AFB) and Cartridge Based Nucleic Acid Amplification Test (CBNAAT) was negative. No growth was seen on blood culture. Based on high clinical suspicion and CORADS score, possibility of COVID-19 was kept. She was treated on lines of moderate illness with steroids (i.v. dexamethasone 6 mg twice daily), prophylactic anticoagulation (LMWH 0.4 mL once daily), and supplemental oxygen therapy. She reported worsening of symptoms on third day.

On evaluation, ECG was normal but CXR showed worsening. She was shifted on NRM (FiO_2-0.08, Flow-12 LPM). CTPA showed

thrombus involving bilateral pulmonary arteries and right inferior pulmonary vein [Table/Fig-3a,b]. She was started on LMWH at therapeutic doses (0.6 mL S/C twice a day) and respiratory support was continued. She showed gradual improvement. She was discharged after two weeks on rivaroxaban but lost to follow-up.

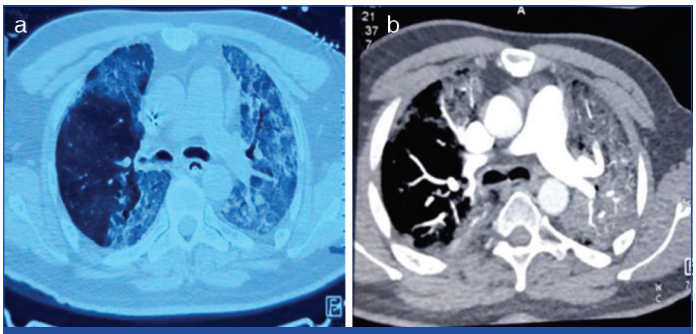


[Table/Fig-3]: a) CECT thorax; lung window showing bilateral patches of consolidation primarily sub-pleural; b) Mediastinal window: Pulmonary thrombus involving bilateral pulmonary arteries and right inferior pulmonary vein.
CECT: Contrast-enhanced computed tomography

Case 6

A 49-year-old male presented with complaints of fever, SOB and cough for 15 days. RT-PCR for COVID-19 was negative. On admission vitals were; BP-100/70 mmHg, PR-99/min and SpO_2 85% on RA. Laboratory investigations showed anaemia (Hb 9.8 g/dL) and raised TLC (14500/µL; lymphocytes 11%, granulocytes 85%) with normal renal and liver function tests. Nasopharyngeal Swab (NPS) for H1N1 influenza was negative and IgM antibodies for typhoid, leptospirosis and scrub typhus were not detected. Sputum for CBNAAT was negative. CORADS score on HRCT chest was 5/6.

He was treated as probable case of severe COVID-19 illness with steroids (dexamethasone; 8 mg i.v. twice a day) and LMWH (0.6 mL twice a day). The patient was put on high flow nasal cannula (HFNC; FiO_2-1.0, Flow-40 LPM) for respiratory support. In view of persistent respiratory distress, he was initiated on mechanical ventilator as per ARDS-net protocol. VD-USG of lower limbs and echocardiography was normal. CTPA chest showed bilateral pneumonia and partial thrombosis of right pulmonary artery [Table/Fig-4a,b]. He was continued on ventilator (ratio of arterial oxygen partial pressure to fractional inspired oxygen; P/F ratio-180) and discharged after 56 days on rivaroxaban. Follow-up CT after three months showed no evidence of residual thrombosis and the patient was doing well.



[Table/Fig-4]: a) CECT thorax; lung window showing bilateral patchy consolidation with peripheral distribution; b) Mediastinal window showing partial thrombosis of right pulmonary artery; anterior segmental branch. (Images from left to right)
CECT: Contrast enhanced computed tomography

DISCUSSION

In this series, three out of six patients had PTE while one each had MI and cerebellar infarct, respectively. Estimated incidence of ischaemic stroke and MI in COVID-19 is 0.9-4.6%, and 1.1-8.9%, respectively [1,3,7,9]. In a meta-analysis, pooled incidence of PTE was 21% with higher rates in Intensive Care Unit (ICU) than non ICU patients [4]. Pulmonary Embolism (PE) patients were older, with lower P/F ratios and higher levels of D-dimer and C-Reactive Protein (CRP) [5]. Two patients had no underlying risk factors for PE in this series. Lari E et al., also reported severe vascular complications in healthy individuals [2]. Out of three patients who presented with PE, only one had evidence of DVT in this series. These findings were consistent with a study from Germany [10]. So, pulmonary thrombosis rather than embolism may be the underlying pathology in such cases and can occur despite thromboprophylaxis [10,11].

Several markers like CRP and D-dimer, P/F ratios and VD-USG have been utilised to rule out DVT, however none could be finalised for routine screening of CAC. CRP at admission was found to be one of the strongest predictors for developing PE in a multivariate analysis, but being a non-specific inflammatory marker, it is of limited utility [5,6]. The sensitivity and specificity of D-dimer levels at 3 µg/mL was 76.9% and 94.9%, respectively with negative predictive value (NPV) of 92.5% to predict venous thromboembolism [12]. Several other studies found that higher D-dimer levels correlated with lower P/F ratios, higher CRP levels and worse outcomes [5,7]. Coagulation/inflammatory markers like ferritin, D-dimer, Lactate Dehydrogenase (LDH) and Interleukin-6 (IL-6) levels could not be assessed due to lack of availability in the institution. However, all the patients presented in this series had positive CRP levels (qualitative assay). All the patients were hypoxemic at the time of referral from peripheral centres. Each of them was put on appropriate oxygen delivery device at admission, only one developed ARDS who was put on ventilator and survived later. VD-USG is less reliable in patients without symptoms of DVT; sensitivity 50% as opposed to >90% in symptomatic patients [13]. In this series also, only one patient who had symptoms of DVT was detected on VD-USG. The direct cause of deaths in this series was most likely CAC.

Two out of six patients in this series were managed on clinico-radiological grounds. As the virus advances towards alveoli, it may be undetectable in NPS, however can be detected on bronchoalveolar lavage [14]. So NPS negativity should not deter the clinician to suspect and treat patients as COVID-19.

The pathophysiology of CAC is multifactorial. Virus induced endothelitis, cytokine release syndrome and formation of NET generate prothrombotic milieu in pulmonary and extra-pulmonary vascular beds. Use of mechanical ventilation, central venous catheters and immobilisation also play a role in CAC [4-6]. The CAC may be under-reported due to lack of knowledge and infrastructural/financial constraints especially in developing countries.

CONCLUSION(S)

Thromboembolic complications of COVID-19 are a major cause of morbidity and mortality. Old age, severe illness and co-morbidities are common risk factors. However, clinicians should be aware of the possibility of unusual thromboembolic presentations in relatively young and healthy individuals. In view of the lack of affordable objective markers with high sensitivity and specificity, high degree of clinical suspicion should be adopted in diagnosing CAC. Long term impact of thromboembolic and cardiovascular complications is largely unknown and warrants further analysis.

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