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CASE SERIES
Heart failure

Left ventricular mural thrombi with multisystem thrombosis in patients with COVID-19 and myocardial injury: a case series

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Background Cardiovascular and thromboembolic complications have been reported in patients with Coronavirus disease-2019 (COVID-19)-related severe respiratory distress syndrome. Although myocarditis associated with COVID-19 pneumonia has been described, evidence of left ventricular (LV) mural thrombi with other multisystem events has not been reported.

Case summary We report two cases with severe COVID-19 pneumonia and myocardial injury with large LV thrombi and other multisystem thrombotic events. The first patient represents an unusual case of large LV apical thrombus without concordant regional wall motion abnormality and mildly reduced LV function. A subsequent inferior ST-elevation myocardial infarction (STEMI) was likely related to either an embolic event or *in situ* coronary thrombosis. We could not ascertain whether the acute right ventricular dysfunction was due to *in situ* pulmonary thrombosis or inferior STEMI. The catastrophic cerebrovascular accident was likely an embolic phenomenon. Similarly, the second patient demonstrated multiple large pedunculated thrombi occupying one-third of the LV cavity with moderately reduced LV function. A segmental pulmonary embolism was diagnosed on computed tomography chest, confirming multiple territories of *in situ* thrombosis.

Discussion COVID-19-related inflammatory cytokine release has been linked to activation of coagulation pathways. Marked elevation of ferritin and C-reactive protein levels in both patients were consistent with evidence of a hyperinflammatory state with 'cytokine storm'. Furthermore, the finding of elevated D-dimer levels lends support to the altered coagulation cascade that plausibly explains the multisystem thrombosis observed in our patients. The direct viral endothelial involvement and subsequent endothelial dysfunction may play an important role in the development of thrombosis in different vascular beds, as seen in our patients.

Keywords Left ventricular thrombi • Myocardial injury • COVID-19 • ST-elevation myocardial infarction • Case series

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Learning points

- Left ventricular thrombi are an exceedingly rare manifestation of myocarditis.
- COVID-19-mediated endotheliitis and activation of coagulation pathways have been implicated in thrombosis in different vascular beds.
- Significant rise in D-dimer levels can herald the onset of these catastrophic thromboembolic events in COVID-19 infection which are associated with a dismal prognosis.

Introduction

COVID-19-related respiratory distress syndrome has been associated with myocardial injury and other cardiovascular (CV) complications.[1] The following two patients presented with severe COVID-19 pneumonia and hyperinflammatory state with cardiac injury, left ventricular (LV) mural thrombi, and other multisystem thrombotic events supporting a common pathophysiologic mechanism.

Timeline

Day of hospitalization	Patient 1	Patient 2
Day 0	• A 48-year-old female presented to ED with fever and dyspnoea for 3 days	• A 60-year-old male with schizophrenia brought to the ED with altered mental status and shortness of breath
Days 1–4	• Developed worsening hypoxaemia requiring mechanical ventilation • Laboratory work-up showed elevated D-dimer, C-reactive protein, Troponin T, and ferritin levels	• Noted to have worsening hypoxaemia requiring oxygenation via high flow nasal cannula • Computed tomography (CT) chest revealed peripheral airspace opacities. In addition, filling defects noted in left ventricle and right upper lobe pulmonary artery • Transthoracic echocardiogram confirmed large LV thrombi with moderately reduced LV systolic function
Days 5–8	• New ST-elevations in inferior leads (ST-elevation myocardial infarction) • Echocardiogram showed large mobile, protruding left ventricular apical thrombus and inferior hypokinesis • CT head revealed large left middle and posterior circulation cerebrovascular event with mass effect • Multidisciplinary discussion with patient family and decision made to manage patient conservatively	• Weaned off oxygen supplementation and transferred to the inpatient psychiatry ward

Case presentation

Patient 1

A 48-year-old female with hypertension presented with high-grade fever and dyspnoea. Her maximum temperature was recorded at 38.8°C and oxygen saturation was 86% on room air. Physical exam was remarkable for respiratory distress and diffuse crackles posteriorly. Labs revealed a markedly elevated D-dimer of 8.1 mg/L (<0.5 mg/L), high-sensitivity Troponin T (Hs-Trop T) of 91 ng/L (<14 ng/L), ferritin of 3604 ng/mL (<150 ng/mL), and C-reactive protein (CRP) of 11.8 mg/dL (<0.50 mg/dL). A chest X-ray revealed bilateral diffuse peripheral ground-glass opacities (*Figure 1A*) suggestive of COVID-19 pneumonia that was confirmed via nasopharyngeal swab polymerase chain reaction (PCR). On Day 2, she developed worsening hypoxaemia necessitating mechanical ventilation. She was started on hydroxychloroquine and tocilizumab. Since patient had acute kidney injury with creatinine of 1.8 mg/dL, computed tomography (CT) chest with contrast was deferred. On Day 7, ST-elevations were noted on telemetry and the electrocardiogram (EKG) was suggestive of an acute inferior ST-elevation myocardial infarction (STEMI) (*Figure 1B*). A transthoracic echocardiogram (TTE) revealed a large protruding, mobile LV apical hypodensity consistent with thrombus; LV systolic function was mildly reduced with basal inferior wall hypokinesis, and the right ventricle was dilated and hypokinetic (*Figure 1C and D* and *Videos 1 and 2*). Hs-Trop T was 2550 ng/L and D-dimer increased to >69 mg/L. Given a poor prognosis with refractory hypoxaemia and worsening kidney function, multidisciplinary consultation was held with family and decision was made to manage medically with antithrombotic therapy. On Day 8, resolution of EKG changes was noted. However, an abnormal neurologic exam prompted an urgent CT head that documented a large ischaemic left hemispheric stroke in the middle and posterior cerebral artery distributions with midline shift (*Figure 1E*). The exam and cerebral perfusion scintigraphy scan were subsequently consistent with brain stem death. As per the family's wishes, patient was made hospice and ventilator was disconnected.

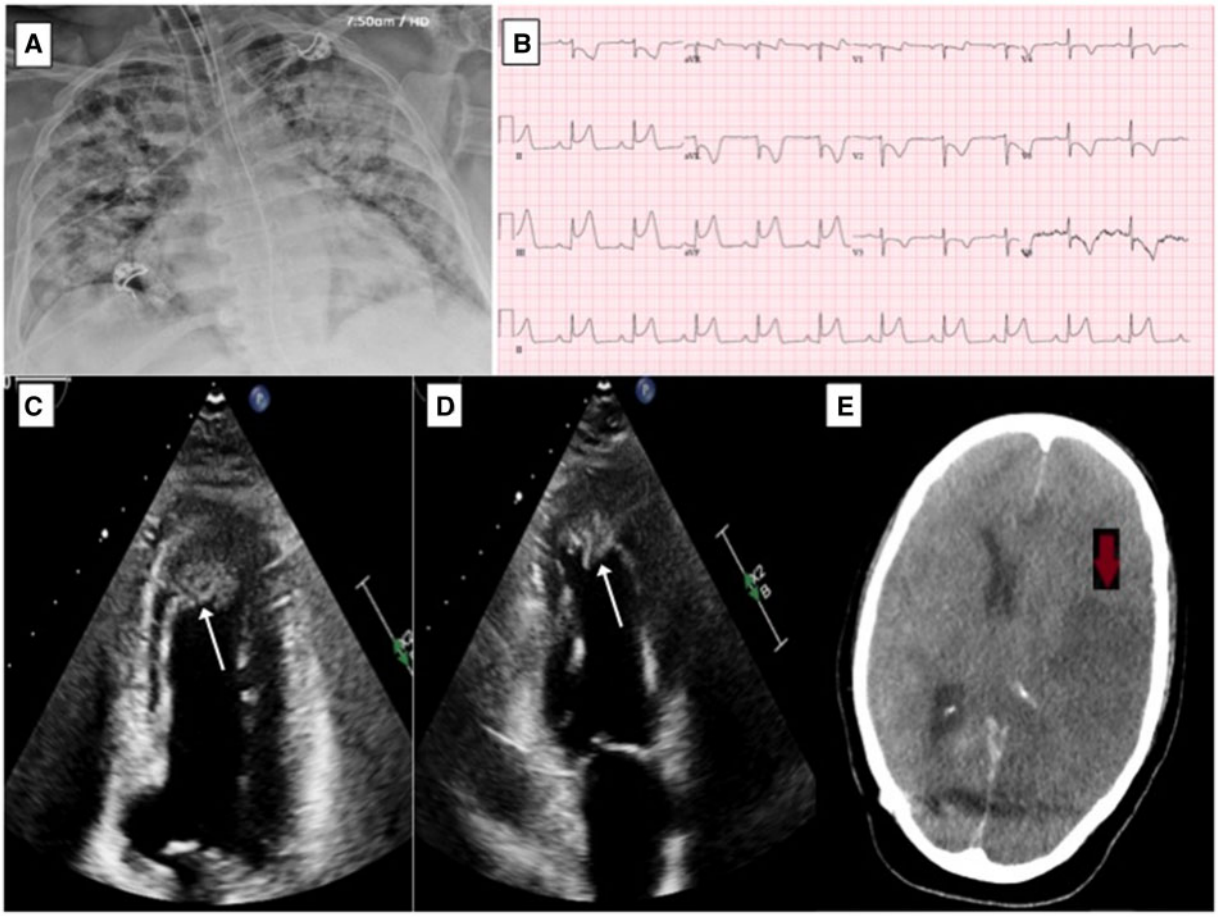
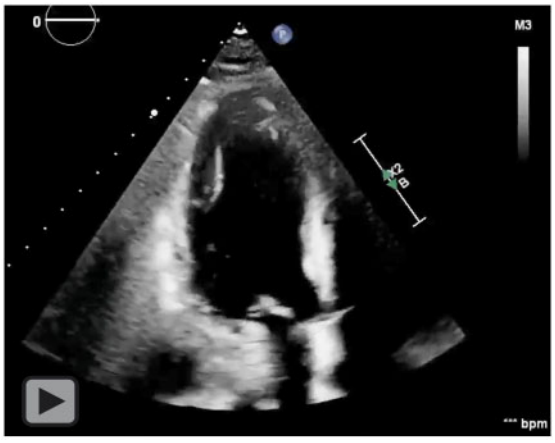
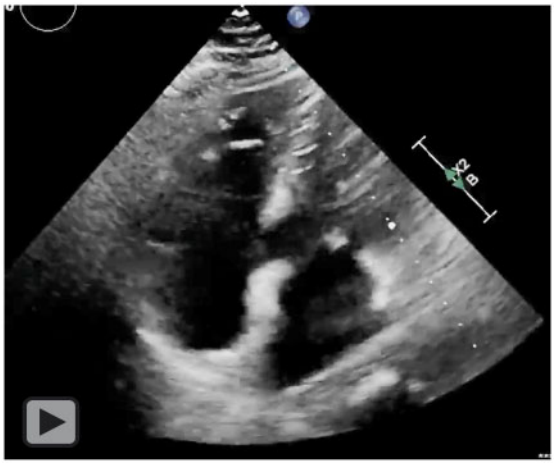


Figure 1 (*A*) Anteroposterior chest film demonstrating diffuse bilateral infiltrates. (*B*) Electrocardiogram showing an inferoposterior ST-elevation myocardial infarction. (*C* and *D*) Transthoracic echocardiogram with apical four- and two-chamber views demonstrating layered, protruding apical thrombus (white arrows) measuring 1.8 cm × 2.4 cm. (*E*) Computed tomography head showing a large ischaemic cerebrovascular accident in middle and posterior cerebral circulation with midline shift.



Video 1 Apical two-chamber view demonstrating a layered left ventricular apical thrombus (Patient 1).



Video 2 Apical four-chamber right ventricle focused view demonstrating a dilated and hypokinetic right ventricle (Patient 1).

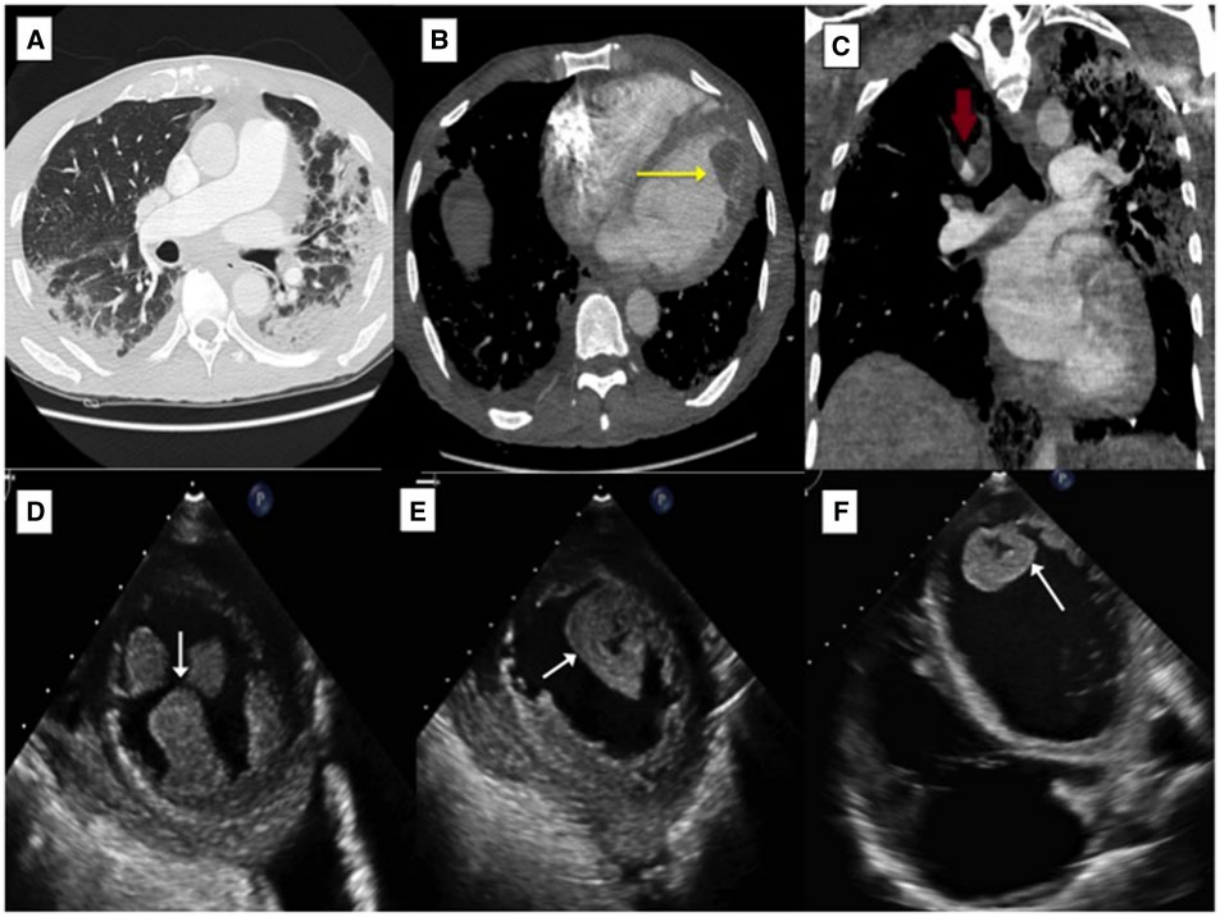
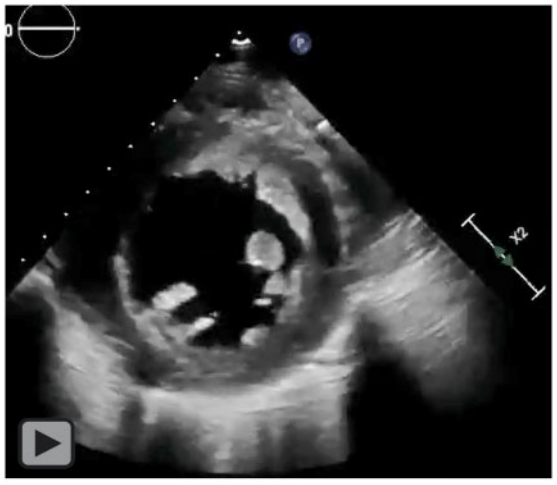


Figure 2 Computed tomography chest with (*A*) axial section showing diffuse peripheral bilateral ground-glass opacities, (*B*) filling defect in the left ventricular cavity (30 Hounsfield units) suggestive of a thrombus, and (*C*) coronal section demonstrating a right upper lobe filling defect. (*D–F*) Transthoracic echocardiogram views showing multiple pedunculated thrombi attached at the anterior, lateral, and inferior walls largest measuring 3 cm × 3 cm with central clearing.



Video 3 Parasternal short-axis view at papillary muscle level showing multiple left ventricular thrombi (Patient 2).

Patient 2

A 60-year-old male with history of hypertension and schizophrenia presented to the hospital after being found altered on the street. He was febrile to 38.2°C and required oxygen via high flow cannula (oxygen saturation 84% on room air). Labs revealed an elevated D-dimer of 12.9 mg/L, ferritin of 700 ng/mL, and CRP of 4.5 mg/dL. Troponin I trend was 0.77–0.29–0.20 ng/mL (<0.03 ng/mL) and brain natriuretic peptide was 1100 pg/mL (<100 pg/mL). EKG revealed sinus rhythm with signs of LV hypertrophy and prolonged QTc of 513 ms. CT head was negative for any acute intracranial pathology. CT chest demonstrated multifocal peripheral airspace opacities (*Figure 2A*) consistent with COVID-19 pneumonia that was later confirmed via nasopharyngeal swab PCR. Moreover, filling defects were noted within the LV cavity and segmental right upper lobe pulmonary artery consistent with mural thrombus and pulmonary embolism (PE), respectively (*Figure 2B and C*). TTE revealed moderately reduced LV systolic function and multiple large pedunculated thrombi (largest measuring 3 × 3 cm) attached at the apex, apical anterior, inferior, and lateral walls (*Figure 2D–F*, *Video 3*, and Supplementary material online, *Video S1*). Coronary

CT angiography was limited secondary to motion artefact due to the patient's mental status, however, calcium score was zero. The patient was admitted to the COVID-19 telemetry floor and managed with hydroxychloroquine, steroids, and heparin. He was subsequently weaned off oxygen and transferred to a psychiatry unit.

Discussion

The pro-inflammatory cytokine release in patients with COVID-19 has been linked to substantial risks of cardiac injury and other thromboembolic complications.[2] In a recent meta-analysis of critically ill patients with COVID-19 infection, the rates of venous and arterial thromboembolism were 31% and 5%, respectively.[3] Myocardial injury in addition has been associated with worse prognosis in these patients.[4]

In both of our cases, overt signs of myocardial injury were noted with cardiac biomarker elevation upon presentation suggestive of myocarditis, although magnetic resonance imaging evidence is lacking. Large LV mural thrombi and accompanying multisystem thrombotic events further ensued and have not been reported in patients with COVID-19 to date.[5] Indeed, LV thrombus is a rare manifestation of myocarditis, except in eosinophilic myocarditis.

The first patient represents an unusual case of large LV apical thrombus without concordant regional wall motion abnormality and only mildly reduced LV function. A subsequent inferior STEMI was likely related to either an embolic event or *in situ* coronary thrombosis. We could not ascertain whether the acute right ventricular dysfunction was due to *in situ* pulmonary thrombosis or infarction from the inferior STEMI. The catastrophic cerebrovascular accident was likely an embolic phenomenon, although the possibility of large-vessel thrombosis cannot be ruled out. Similarly, the second patient demonstrated multiple large pedunculated thrombi occupying one-third of the LV cavity with moderately reduced LV function. Additionally, a segmental PE was documented on a CT chest, thus confirming multiple territories of *in situ* thrombosis.

COVID-19-related inflammatory cytokine release has been linked to activation of coagulation pathways.[6] Marked elevation of ferritin and CRP levels in both patients were consistent with evidence of a hyperinflammatory state with 'cytokine storm'. Furthermore, the finding of elevated D-dimer levels lends support to the altered coagulation cascade that plausibly explains the multisystem thrombosis observed in our patients. Interestingly, D-dimer levels increased >8 times compared to admission levels in the setting of STEMI and stroke in the first patient. Not surprisingly, elevated D-dimer levels in patients with COVID-19 have been shown to portend a poor prognosis.[7] While the understanding of mechanisms underlying CV involvement in context of interactions between inflammatory and coagulation pathways continues to evolve, direct vascular inflammation and endotheliitis have also been described in COVID-19 patients.[8] Direct viral endothelial involvement and subsequent endothelial dysfunction might play an important role in the development of thrombosis in different vascular beds, as seen in our patients. Altogether, these findings likely explain the disease progression and poor survival rate in patients with severe COVID-19 and myocardial injury. Accordingly, guideline statements have recommended therapeutic parenteral anticoagulation in hospitalized patients with suspected or confirmed thromboembolism.[9] However, pending results from randomized controlled trials, clear guidance regarding intensity, and duration of anticoagulation is lacking. Finally, several trials are underway to investigate the optimal regimen (e.g. half or full-dose therapeutic anticoagulation vs. standard of care, or direct oral acting anticoagulant) for thromboprophylaxis in such high-risk patients.

Conclusions

We report unusual presentations of severe COVID-19 infection complicated by LV mural thrombi and other multisystem thrombotic events. Both patients had evidence of cardiac injury and thus highlight the extreme vigilance needed to monitor for *in situ* thrombosis and other thromboembolic events in patients admitted with severe COVID-19. Multisystem thrombosis is likely related to both disseminated intravascular coagulation as well as direct endothelial inflammation. Measurement of D-dimer levels might assist in decision-making regarding further investigations and treatment in these patients.

Lead author biography

Aakash Garg is currently pursuing interventional cardiology training at the Mount Sinai Hospital in New York. He finished his fellowship in cardiology at the Newark Beth Israel Medical Center. His research interests include antithrombotic therapy in coronary artery disease and outcomes research in cardiac interventions.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: Approval from the Institutional Review Board was obtained for the publication of this manuscript. Patient 1: the patient died during admission and was therefore unable to consent to publication of this case report. Extensive attempts were made to identify a next of kin without success. Patient 2: the patient lacked capacity was unable to give consent to publication of this case report. Extensive attempts were made to identify a next of kin without success.

Conflict of interest: None declared.

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