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CASE REPORT
Other

Recurrent massive pulmonary embolism following catheter directed thrombolysis in a 21-year-old with COVID-19: a case report

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Background Coronavirus Disease-2019 (COVID-19) has been associated with increased incidence of pulmonary embolism (PE), even among patients at low risk for venous thrombo-embolic (VTE) events.

Case summary We present the case of a 21-year-old male, with no previous medical history, who presented with cough, fevers, shortness of breath, pleuritic chest pain, and 1 day of dizziness with near syncope as well as acutely worsened dyspnoea. He was subsequently diagnosed with COVID-19 and massive PE. He underwent successful catheter-directed thrombolysis (CDT), and his clinical status improved. One day following initial CDT, he developed acute respiratory failure and hypotension and was diagnosed with recurrent massive PE. He was treated with repeat CDT and extracorporeal membrane oxygenation (ECMO) to provide time for right ventricular recovery. The patient was able to be weaned off ECMO after 9 days and was eventually extubated and discharged to an acute rehabilitation facility.

Discussion Beyond COVID-19, no hypercoagulable risk factors were identified despite thorough investigation. This case highlights the thrombogenic potential and morbid sequelae of SARS-CoV-2 infection, even in young patients. It also highlights the use of CDT and ECMO among patients with massive PE and COVID-19. To date, this is the youngest reported patient to develop massive PE in the setting of COVID-19.

Keywords COVID-19 • Pulmonary embolism • Massive pulmonary embolism • Catheter-directed thrombolysis • COVID-19 associated hypercoagulability • ECMO • Case report

Learning points

- Pulmonary embolism (PE) is associated with Coronavirus Disease-2019 (COVID-19) and should be suspected in any patient with haemodynamic collapse regardless of their age, clinical trajectory, or anticoagulation status.
- Careful attention should be paid to initiation and dosing of anticoagulation in patients with COVID-19. This is particularly true of obese patients.
- Catheter-directed thrombolysis and extracorporeal membrane oxygenation should be considered in critically ill patients with massive PE and COVID-19.

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Introduction

Since the emergence of Coronavirus Disease-2019 (COVID-19), an association between Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection and coagulopathy has been noted.[1] Pulmonary embolism (PE) is widely described in this context, even among patients at low risk for venous thromboembolic (VTE) events.[2] We illustrate the case of a 21-year-old male, who presented with COVID-19 and a sub-massive PE with later development of massive-PE requiring catheter directed thrombolysis (CDT), extracorporeal membrane oxygenation (ECMO), and repeat CDT for recurrent massive PE.

Timeline

Hospital day(s)	Significant event
1–2	Patient presented to the emergency department and was diagnosed with Coronavirus Disease-2019 (COVID-19) by PCR and acute sub-massive pulmonary embolism (PE) by CTPA; unfractionated heparin (UFH) was initiated. Twelve hours into hospital course, the patient became hypotensive, was diagnosed with massive PE and underwent catheter-directed thrombolysis (CDT) of the bilateral pulmonary arteries.
3	Patient improved clinically; plans made for discharge.
4	Patient developed acute respiratory failure and hypotension. Patient was intubated and developed cardiac arrest; return of spontaneous circulation (ROSC) was obtained following cardiopulmonary resuscitation (CPR) and electrical shock. Vasopressors and veno-arterial extracorporeal membrane oxygenation (ECMO) were initiated at bedside. Pulmonary artery angiogram demonstrated interval worsening of bilateral pulmonary emboli compared to index computed tomography pulmonary angiogram, confirming diagnosis of recurrent massive PE. Repeat CDT was performed.
5–9	Ventilation parameters improved, vasopressors were discontinued, and weaning of ECMO began. Venous duplex ultrasound demonstrated deep venous thrombus of the right femoral vein and right popliteal vein. An inferior vena cava (IVC) filter was placed. UFH transitioned to low-molecular weight heparin.
10	Repeat pulmonary artery angiogram demonstrated improvement in emboli burden. Patient successfully weaned from ECMO and decannulated.
11–52	Hospital course was notable for septic shock treated and development of a right thigh haematoma with compartment syndrome requiring surgical debridement on hospital Day 40. Post-operatively, the patient was transitioned to rivaroxaban. On hospital Day 52, the patient was discharged to an acute rehabilitation facility.

Case presentation

An obese 21-year-old male with no other past medical history presented to the emergency department (ED) with 3 days of cough, fevers, shortness of breath, pleuritic chest pain, and 1 day of lightheadedness with near syncope as well as acutely worsened dyspnoea. He denied contact with sick persons, exertional chest pain, weight loss, night sweats, abdominal pain, changes in bladder or bowel habits, and recent travel, surgery, or prolonged immobilization. Upon arrival, he was febrile (38.9°C), tachycardic (121 beats per minute), normotensive (104/66 mmHg), and hypoxic saturating 82% on room air, however, improved to 100% with non-rebreather mask at 15 L/min.

Obesity: body mass index (BMI) 37.

This patient's presentation with chest pain, dyspnoea, and near syncope preceded by cough and fever in the midst of a global pandemic raised concerns for COVID-19 and community-acquired pneumonia as well as pneumothorax and pulmonary embolism.

Severe Acute Respiratory Syndrome Coronavirus 2 nasopharyngeal qualitative polymerase chain reaction (PCR) was positive. electrocardiogram (ECG) demonstrated evidence of right heart strain as well as S wave in lead I, Q wave and inverted T wave in lead III (S1Q3T3), a pattern associated with acute PE (*Figure 1*). Point of care ultrasound demonstrated right ventricular free wall hypokinesis with preserved apical contractility (McConnel's sign), also consistent with PE. Initial D-Dimer was elevated at 3.71 mcg/mL (Ref. range ≤0.49), troponin-T was elevated at 0.04 ng/mL (Ref. range ≤0.00), and pro-BNP NT was elevated at 4573 pg/mL (Ref. range ≤125). A computed tomography pulmonary angiogram (CTPA) demonstrated pulmonary emboli involving the bilateral pulmonary arteries, including the central, segmental, and subsegmental branches. There was also enlargement of the pulmonary trunk and flattening of the interventricular septum, with right ventricle to left ventricle ratio of 1.4 to 1 (*Figure 2*).

The patient was admitted to the intensive care unit (ICU) on high-flow nasal cannula and intravenous (IV) unfractionated heparin (UFH) infusion (goal PTT 60–80 s) with stable vital signs. Twelve hours after initial presentation, the patient became increasingly hypoxic and persistently hypotensive with systolic blood pressure <90 mmHg. At this point, he was presumptively diagnosed with massive PE, and urgently underwent CDT of the bilateral pulmonary arteries utilizing the EKOS™ Endowave Infusion Catheter System (1 mg/h tissue plasminogen activator (tPA) per side over 6 h). Intravenous heparin infusion was continued (goal PTT 40–60 s during tPA infusion, 60–80 s post-tPA infusion). Following CDT, the patient improved clinically and was transferred to the general medicine floor on hospital Day 3 with minimal supplemental oxygen and plan to discharge with oral anticoagulation.

On hospital Day 4, the patient was initially normotensive with blood pressure 114/64 mmHg and saturating 99% on 2 L/min of oxygen via nasal cannular when he developed acute respiratory failure with oxygen saturation of 65% requiring non-re-breather mask and hypotension with blood pressure 70/30 mmHg. The patient was subsequently intubated and developed cardiac arrest regaining spontaneous circulation after two rounds of cardiopulmonary resuscitation and one electrical shock. Vasopressor support was initiated with

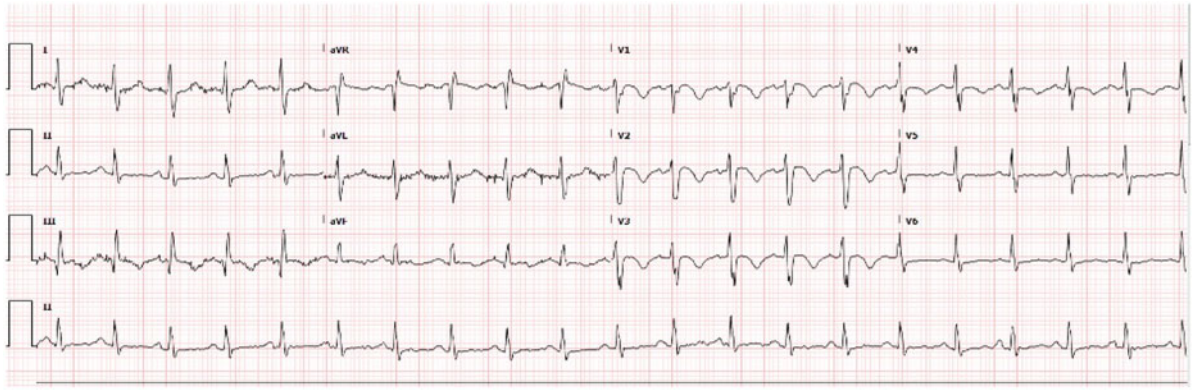

Figure 1 Initial ECG. ECG on arrival demonstrating evidence of right heart strain as well as S wave in lead I, Q wave and inverted T wave in lead III (S1Q3T3), a pattern associated with acute pulmonary embolism.

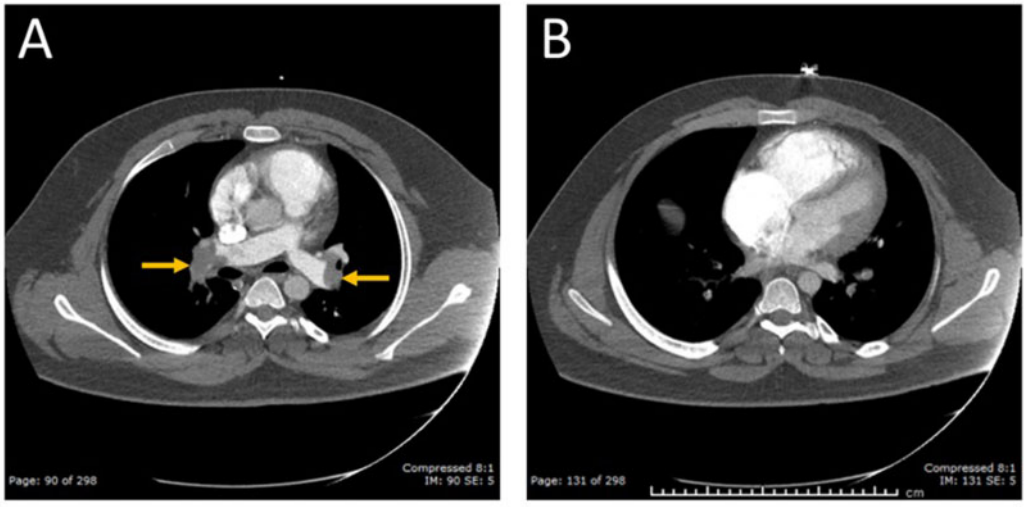

Figure 2 Initial computed tomography pulmonary angiography. (*A*) CTPA demonstrating large, bilateral pulmonary emboli (yellow arrows). (*B*) CTPA demonstrating flattening of the interventricular septum and increased right ventricle:left ventricle ratio, suggestive of right ventricular strain in the setting of pulmonary embolism.

norepinephrine, epinephrine, vasopressin, and phenylephrine. Due to persistent haemodynamic instability, veno-arterial extracorporeal membrane oxygenation was initiated at bedside. Recurrence of massive PE was suspected, but a repeat CTPA could not be obtained due to clinical instability. Instead, the patient was taken to the catheterization laboratory where a pulmonary angiogram demonstrated bilateral pulmonary emboli with interval worsening of clot burden compared to index CTPA (*Figure 3*). Repeat CDT of the bilateral pulmonary arteries was performed (2 mg/h tPA per side over 6 h) with continuous systemic IV UFH infusion (goal PTT 50–60 s during tPA infusion, 60–80 s post-tPA infusion).

Over the next 48 h, ventilation parameters improved, and vasopressors were discontinued. Repeat pulmonary angiography demonstrated significant improvement in the right central pulmonary embolism, with residual obstruction of the left central pulmonary artery (*Figure 4*). Venous duplex ultrasound was then performed demonstrating non-occlusive thrombus of the right femoral vein and right popliteal vein. An inferior vena cava filter was placed, and the patient's anticoagulation regimen was transitioned from UFH to low-molecular-weight heparin (LMWH) (Enoxaparin, 1 mg/kg every 12 h) due to concern for failure of anticoagulation. Hypercoagulable workup consisting of Beta-2 Glycoprotein, Cardiolipin, and Phospholipid Antibodies as well as Prothrombin A and Factor V Leiden gene mutations was unremarkable. The patient was successfully weaned from ECMO on hospital Day 10 and extubated on hospital Day 31.

The remainder of the hospital course was notable for septic shock treated with broad spectrum antibiotics and development of a right thigh haematoma and compartment syndrome requiring surgical debridement on hospital Day 40. Postoperatively, the patient was

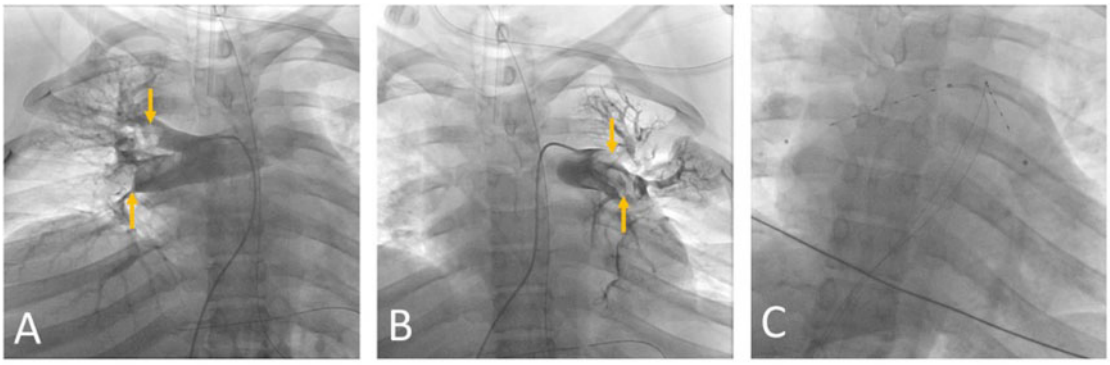

Figure 3 Initial pulmonary angiography and catheter directed thrombolysis. (*A*) Right pulmonary angiography demonstrating pulmonary emboli (yellow arrows). (*B*) Left pulmonary angiography demonstrating pulmonary emboli (yellow arrows). (*C*) Dual ultrasonic thrombolysis catheters in bilateral pulmonary arteries.

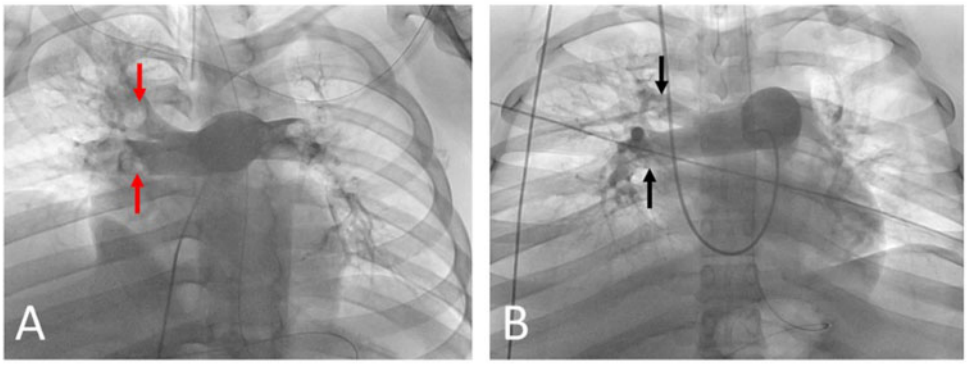

Figure 4 Subsequent pulmonary angiography and catheter directed thrombolysis. (*A*) Bilateral pulmonary angiography demonstrating persistent pulmonary emboli after catheter-directed thrombolysis (red arrows). (*B*) Bilateral pulmonary angiography demonstrating reduced thrombus burden and improved flow in the right pulmonary artery following repeat catheter-directed thrombolysis (black arrows). Neither the left pulmonary embolism nor arterial flow was significantly improved.

transitioned to rivaroxaban 15 mg twice daily for 21 days and 20 mg once daily thereafter. On hospital Day 52, the patient was discharged to an acute rehabilitation facility.

The patient returned home 67 days after admission and was able to perform activities of daily living independently. The patient remained anticoagulated on rivaroxaban 20 mg daily and had no major adverse events 4 months following discharge.

Discussion

Massive PE is increasingly recognized as a significant cause of mortality in COVID-19. One systematic review estimates the incidence and mortality rate of PE in COVID-19 patients to be as high as 15% and 45%, respectively.[3] A study involving postmortem examination of COVID-19 patients demonstrated that massive PE was the cause of death in 33% (4/12), with thrombi originating from lower extremity.[4] Notably, all four patients who died were markedly obese (BMI 34.4–38.8).

The frequency of thrombosis and PE in patients with COVID-19 highlights the need for early and appropriate anticoagulation. A retrospective analysis of 4400 adults with COVID-19 demonstrated that prophylactic and therapeutic anticoagulation was associated with a roughly 50% reduction in mortality when initiated within 48 h of admission, compared to no anticoagulation.[5] For COVID-19 patients, the International Society on Thrombosis and Haemostasis (ISTH) currently recommends standard dose prophylaxis for all admitted patients, intermediate dose prophylaxis for critically ill patients and those with acute respiratory distress syndrome, and therapeutic dose anticoagulation for patients with confirmed or presumed venous thromboembolism. The ISTH cautions that for obese patients, the standard doses of UFH and LMWH are likely insufficient, and a 50% dose increase for thromboembolic prophylaxis should be considered.[6] However, treatment failure and recurrence of venous

thromboembolism despite anticoagulation appears to be common. One single-centre case series of COVID-19 patients admitted to the ICU identified PE in 22 (20.6%). At the time of diagnosis, 20 of the 22 were receiving appropriate antithrombotic treatment with UFH or LMWH.[7]

At present, there are no large-scale studies to guide management of PE in COVID-19. Case reports have yielded mixed results with varying approaches including mechanical thrombectomy, CDT, systemic thrombolysis, and anticoagulation alone.[8–10] Massive PE in the setting of COVID-19 represents a unique and challenging clinical entity which may benefit from therapies such as CDT and/or ECMO. The role and efficacy of CDT in treating massive PE is an area of ongoing debate, while the use of ECMO in the setting of COVID-19 continues to evolve.[11,12]

At our centre, we have experienced favourable outcomes in treating massive PE with CDT in carefully selected patients. In addition, we have found that patient with massive PE occasionally require ECMO for temporary support while awaiting right ventricular recovery. Furthermore, we were aware that ECMO had been utilized with positive results in treating severe cases of COVID-19. These factors along with the patient's rapid deterioration following his first massive PE, guided the decision to choose CDT (with ECMO as a bailout option) over systemic thrombolysis. While there are no high-quality comparisons of systemic thrombolysis vs. CDT, multiple large-scale studies have demonstrated the efficacy and safety of CDT.[13,14] Moreover, a large retrospective study showed that CDT was associated with decreased in-hospital mortality and intracranial Haemorrhage when compared to systemic thrombolysis.[15] Localized delivery of thrombolytic agents may help alleviate concerns about dosing adequacy, particularly in obese patients.

Conclusions

This case highlights the thrombogenic potential and morbid sequelae of SARS-CoV-2 infection, even in young patients. To date, this is the youngest reported patient to develop massive PE in the setting of COVID-19. Despite the severity of his illness, the patient had an excellent clinical outcome, demonstrating that CDT and ECMO can be used effectively in carefully selected patients. Given the growing body of evidence suggesting that patients with COVID-19 are prone to thrombosis and recurrent thrombo-embolic events despite appropriate anticoagulation, more research is required to determine best clinical practices.

Lead author biography

Julian Hirschbaum is a 4th-year resident at LAC+USC Medical Center in Los Angeles completing his residency in the combined specialties of Internal Medicine and Pediatrics. He is interested in congenital heart disease and providing transitional care to underserved adolescents and young adults living with congenital heart disease. He plans to pursue a fellowship in Pediatric Cardiology followed by a focus in Adult Congenital Heart Disease. In addition to his interest in Cardiology, he is also focused on primary healthcare for underserved populations, global health, and improving access to healthcare in rural areas through the training of community health workers.

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Supplementary material

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

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

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

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