Acute submassive pulmonary embolism after SARS-CoV-2 infection: a case report of reinfection or prolonged hypercoagulable state

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Background
Coronavirus disease 19 (COVID-19) reinfection has been a topic of discussion with data still emerging. Viral antibodies are known to develop upon initial infection; however, it is unclear the amount of protection this confers against reinfection. Additionally, COVID-19-associated coagulopathy (CAC) is a well-documented phenomenon; however, there are no high-quality studies to support the treatment of outpatients beyond standard indications of venous thromboembolism (VTE) prophylaxis. This case describes a patient with either COVID-19 reinfection or prolonged course of CAC resulting in pulmonary embolism (PE).

Case summary
A 40-year-old healthy man presented with fever and cough. He tested positive for COVID-19 and was sent home to self-quarantine. His symptoms resolved and repeat COVID-19 testing returned negative. Two months later, he developed dyspnoea on exertion and syncope. Computed tomography with PE protocol demonstrated acute bilateral PE, and repeat COVID-19 testing returned positive. He was escalated to catheter-directed thrombolysis, but prior to the procedure went into cardiopulmonary arrest. Cardiopulmonary resuscitation was initiated and full-dose systemic alteplase was administered. Cardiothoracic surgery was consulted for consideration of veno-arterial extracorporeal membrane oxygenation; however, return of spontaneous circulation was unable to be achieved.

Discussion
This case raises the question of COVID-19 reinfection and prolonged risk of VTE due to CAC. We believe the patient was reinfected with COVID-19 provoking his PE; however, a single COVID-19 infection causing a prolonged course of CAC is possible. Until better data exists, decisions regarding outpatient prophylaxis must be individualized to weigh the risks of bleeding against the risk of thrombosis.

Keywords
COVID-19 • SARS-CoV-2 • Pulmonary embolism • Reinfection • Coronavirus disease 19-associated coagulopathy • Case report
Introduction

Reinfection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been a topic of recent discussion with data still emerging from the literature. Antibodies to the virus are known to develop upon initial infection with SARS-CoV-2; however, it is unclear as to the amount of protection this confers against reinfection. The presence of these antibodies raises the question of post-infection immunity with SARS-CoV-2 in particular, as other viral pathogens such as influenza have not been shown to produce a durable immune response after initial infection. To date, there have only been a small number of animal studies suggesting a blunted immune response to the re-exposure of SARS-CoV-2, and currently, there are ongoing studies investigating a possible therapeutic role of donor antibodies in humans using convalescent plasma for the treatment of coronavirus disease 19 (COVID-19) pneumonia.

Additionally, COVID-19-associated coagulopathy (CAC) is a well-documented phenomenon with an incidence of 31%. Therapeutic anticoagulation is indicated for the treatment of diagnosed CAC-related venous thromboembolism (VTE). However, prophylactic anticoagulation regimens in patients without diagnosed or suspected VTE are variable. In patients hospitalized with COVID-19, daily coagulation testing is routinely performed, including prothrombin time, activated partial thromboplastin time, D-dimer, and fibrinogen that may guide prophylactic anticoagulation therapy. Early studies suggest that prophylactic doses of anticoagulation in the inpatient setting have been associated with improved outcomes.

In contrast, the incidence of VTE in patients discharged after SARS-CoV-2 infection is not known. Therefore, the guidelines for VTE prophylaxis in the outpatient setting remain controversial and routine coagulation testing in these patients is not done. Under the most recent National Institutes of Health guidelines in the USA, VTE prophylaxis has been reserved for select individuals with COVID-19 pneumonia who have either been discharged from the hospital or have other known thrombotic risk factors. Anticoagulation is continued in these patients for up to 42 days; however, at this time there are no trials that address VTE prophylaxis in outpatients infected with SARS-CoV-2.

This case describes a patient with a prior diagnosis of COVID-19 pneumonia who presented with an acute, submassive pulmonary embolism (PE) 3 months after initial infection. Interval COVID-19 testing was negative. Upon diagnosis of the PE, a third test returned positive, suggesting a case of either COVID-19 reinfection vs. a prolonged course of CAC resulting in PE.

Timeline

Learning points

- It remains unclear how much protection prior infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) confers against repeat infection.
- Coagulopathy due to SARS-CoV-2 may persist for a longer period of time than previously thought, possibly up to 3 months after initial infection.
- It may be beneficial to screen for coagulopathy in SARS-CoV-2 positive patients regardless of clinical stability and treat them with a prolonged course of thromboprophylaxis.
Case presentation

A 40-year-old previously healthy man with a past medical history only notable for a body mass index of 27 presented to the Emergency Department (ED) with several days of fever and cough. He tested positive for SARS-CoV-2 on polymerase chain reaction (PCR) nasopharyngeal swab. His vital signs on examination were notable for a heart rate of 110 beats per minute and a temperature of 38.2°C. His chest X-ray was unremarkable. Given his clinical stability, further labwork was deferred and the patient was discharged from the ED to self-quarantine at home. Over the subsequent 3 weeks, the patient’s symptoms completely resolved. He had repeat COVID-19 testing prior to returning to work, which was negative.

Two months after his negative COVID-19 testing, the patient developed progressive dyspnoea with minimal exertion. He had an episode of syncope which prompted him to return to the ED for further evaluation. On presentation, his blood pressure was 126/99 mmHg, heart rate 122 beats per minute, temperature 37.5°C, and oxygen saturation 97% on room air. Physical examination was notable for tachycardia with regular rhythm, 3/6 holosystolic murmur at the lower left sternal border, positive jugular venous distention to 10 cm, lungs clear to auscultation bilaterally, and no evidence of lower extremity oedema.

Labwork was significant for a troponin of 0.12 ng/mL (normal < 0.02 ng/mL), brain natriuretic peptide of 1321 pg/mL (normal < 100 pg/mL), lactate 2.5 mm/l (normal 0.9–1.7 mm/l), and a D-dimer of 19 041 ng/mL fibrinogen equivalent units (FEU) (normal < 100 ng/mL FEU). Electrocardiogram revealed sinus tachycardia with an S1Q3T3 pattern (see Supplementary Material). Given the significantly elevated D-dimer and history of SARS-CoV-2 infection, a computed tomography angiogram with PE protocol was obtained that demonstrated acute bilateral PE described as a central obstructive clot with acute thrombus and a high obstructive score as defined by a modified Miller score of 15 (see Supplementary Material). Bedside echocardiography revealed severe right ventricular (RV) enlargement (6.5 cm) (Figure 1, Video 1), positive McConnell’s sign, moderate to severe tricuspid regurgitation (Figure 2, Video 2), right ventricular outflow tract velocity time integral (RVOT VTI) of 6.69 cm (normal > 10 cm) (Figure 3), tricuspid annular plane systolic excursion of 10 mm (normal > 18 mm) (Figure 4), and an right ventricular:left ventricular ratio of 2.4 (normal < 1) (Figure 5). Repeat SARS-CoV-2 PCR testing returned positive, and the patient was admitted to the coronary care unit on a heparin infusion.

After a multidisciplinary pulmonary embolism response team discussion, it was recommended that the patient be escalated to catheter-directed thrombolysis given the multiple high-risk features for acute decompensation. Unfortunately, prior to the procedure the patient had an episode of bradycardia and hypoxia followed immediately by cardiopulmonary arrest with pulseless electrical activity (PEA). Cardiopulmonary resuscitation was immediately initiated and full-dose systemic alteplase was administered. Cardiothoracic surgery was consulted for consideration of veno-arterial extracorporeal...
membrane oxygenation. Unfortunately, return of spontaneous circulation was unable to be achieved due to persistent PEA and asystole.

**Discussion**

This case raises the question of SARS-CoV-2 reinfection and prolonged risk of VTE due to CAC. Our patient had known COVID-19 that had clinically resolved with repeat negative testing. The patient’s third test being positive in the setting of an acute PE raises the question of the relationship between his COVID-19 and his coagulopathy. We postulate that the patient was reinfected with SARS-CoV-2, which subsequently may have provoked his PE; however, given the lack of sensitivity of current COVID-19 testing (63–71%), the possibility of a single SARS-CoV-2 infection causing a prolonged course of CAC still remains. We believe that outpatients diagnosed with COVID-19 should undergo a basic work-up for hypercoagulability including testing for Factor V Leiden, protein C and S deficiencies, prothrombin gene mutation, and antithrombin deficiency. In those deemed to be higher risk (i.e. personal history of VTE, family history of VTE, prolonged immobility, known malignancy, etc.), it may be reasonable to consider VTE prophylaxis in the outpatient setting, but further prospective studies are needed. Future studies should address the incidence of SARS-CoV-2 reinfection and the clinical course of CAC before definitive recommendations and guidelines can be established. Without robust data on post-COVID-19 VTE prophylaxis, decisions regarding post-discharge prophylaxis must be individualized to weigh the risks of bleeding against the risk of thrombosis. Nonetheless, until better data exists it is reasonable to apply prior evidence to guide the decision of post-discharge anticoagulation in medically ill patients.

The decision to not give systemic thrombolysis on presentation was because the patient’s initial presentation was consistent with submassive PE (intermediate-high risk). Based on the results of the
PEITHO Trial, we know that thrombolysis for submassive PE is associated with a reduction in hemodynamic decompensation, however at the cost of increased major extracranial bleeding.\textsuperscript{10} As such, we planned a combination strategy of anticoagulation and catheter-directed thrombolysis.

In regards to the use of RVOT VTI in the echocardiographic assessment of this patient’s PE, RVOT VTI has been shown to be associated with low cardiac index and increased risk of PE-related mortality despite normotension in patients with intermediate–high-risk PE.\textsuperscript{11,12} Current risk stratification models lack the positive predictive value to identify patients at highest risk of PE-related mortality, and as such RVOT VTI can be helpful in the risk assessment of patients diagnosed with PE in conjunction with other recognized echocardiographic assessments of RV function and cardiac output.

Lead author biography

Timothy Pow is an internal medicine resident at Loyola University Medical Center. He is in his last year of residency with plans to continue on to cardiology fellowship at William Beaumont Hospital in Royal Oak, MI next year.

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: 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’s next of kin.

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