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LETTER TO THE EDITOR

Clinical-scientific notes

D-dimer negative pulmonary embolus and spontaneous intracranial haemorrhage complicating COVID-19 in a lung transplant recipient

A 22-year-old female university student of Polynesian ethnicity presented to hospital with a 1-day history of severe exertional dyspnoea, on a background of COVID-19 infection diagnosed using polymerase chain reaction testing 4 days prior. She was fully vaccinated (Pfizer, last dose 2 months prior to admission), and received sotrovimab on day 2 of illness. She had a history of bilateral sequential lung transplantation 9 years prior for interstitial lung disease. Her post-transplant course had been uncomplicated; immunosuppression included mycophenolate mofetil, prednisolone and tacrolimus, as well as prophylactic azithromycin and trimethoprim-sulfamethoxazole. There were no identifiable risk factors for, or family history of, venous thromboembolism (VTE) or intracranial haemorrhage (ICH). She was a non-smoker and lived at home with family.

Soon after presentation she developed acute headache, blurred vision and right arm incoordination. This resolved after several minutes. Vital signs, neurological examination (after resolution of the neurological symptoms) and cardiorespiratory examination were normal. Electrocardiography demonstrated new right-axis deviation.

Full blood examination and inflammatory markers were unremarkable. Notably, D-dimer and coagulation studies were normal, and a serum beta-human chorionic gonadotropin was negative. Troponin and brain natriuretic peptide were also negative. A computed tomography (CT) pulmonary angiography (CTPA) was performed due to severe dyspnoea, revealing a right upper lobe pulmonary embolism (PE) with an enlarged right ventricle, indicating submassive PE, with normal lung parenchyma (Fig. 1). The finding of normal lung parenchyma excluded pneumonia and pulmonary oedema. CT of the brain revealed a small right cerebellar subarachnoid haemorrhage, with contrast studies demonstrating no evidence of vascular malformation or venous sinus thrombosis.

An inferior vena caval (IVC) filter was inserted and in consultation with neurosurgery, a low-dose heparin infusion was commenced. An interval 24-h CT of the brain demonstrated resolution of the bleed. She continued to a full recovery and was discharged the following week on direct-oral anticoagulant apixaban. She will be reviewed in the outpatient department with a repeat CTPA, with a view to remove the IVC filter and cease apixaban if the embolus has resolved.

The present case is unique in that it demonstrates a PE with false-negative D-dimer. It also demonstrates simultaneous bleeding and clotting complications of COVID-19. In the absence of any other predisposing risk factors for PE or ICH, we believe both occurred secondary to COVID-19 infection. VTE and spontaneous ICH are both described complications of COVID-19 infection, thought to relate to coagulation disruption and excessive inflammation.[1,2] To our knowledge there is no reported case of both occurring simultaneously in a non-critically ill COVID-19 patient and in the absence of consumptive coagulopathy. Although VTE is a described complication of lung transplantation, this occurs in the early post-transplant period.[3] Given the patient is 9 years post lung transplantation, normally fit and mobile with an uncomplicated post-transplant course, we do not believe she was at increased VTE risk related to her transplant in the absence of other factors such as acute infection, surgery or in-dwelling catheters.

There is no clear consensus for when to investigate a COVID-19 patient for PE. The Well's score,[4] used to risk-stratify patients presenting with PE symptoms in emergency and inpatient settings, would have returned a score of 0 (low pre-test probability), which in combination with negative D-dimer would have led to a recommendation to stop workup. Rare cases have been reported of PE with negative D-dimer.[5,6] To our knowledge, there is no reported case of negative D-dimer with VTE and COVID-19, with previous studies demonstrating

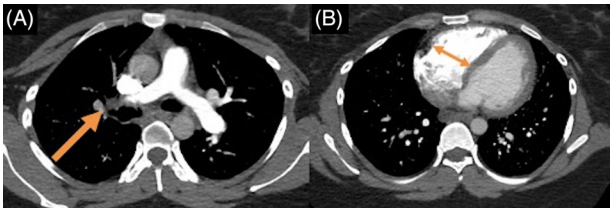

Figure 1 (A) Computed tomography pulmonary angiogram demonstrating a filling defect at the origin of the right upper lobe pulmonary artery branch, suggesting an occlusive right upper lobe pulmonary embolism with (B) right ventricular enlargement suggestive of right heart strain.

100% sensitivity and negative predictive value of D-dimer in excluding PE in COVID-19.[7,8] Other causes for false-negative D-dimers may include small emboli, recent treatment with anticoagulation and a long history of symptoms, and indeed D-dimer cannot exclude PE in cases of high pre-test probability.[5]

This case suggests that D-dimer testing may be unreliable to exclude VTE in a COVID-19 patient, and that PE should be considered in symptoms not clearly explained by other diagnoses. Furthermore, in the absence of diagnostic imaging, this patient's ICH would have been missed and therapeutic anticoagulation initiated for her PE, increasing potential of fatal ICH. There should be a low threshold for neurovascular imaging in COVID-19 patients presenting with headache and neurological symptoms, especially if anticoagulation is indicated for another reason. This case highlights the importance of a low threshold for imaging, which enabled us to identify and appropriately manage these potentially life-threatening complications.

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