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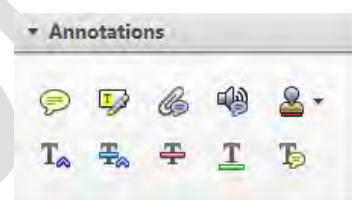


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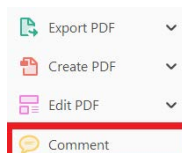
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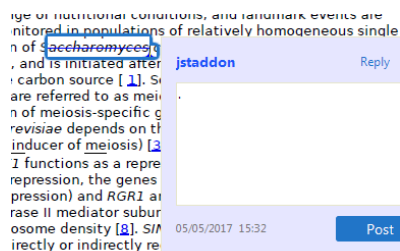
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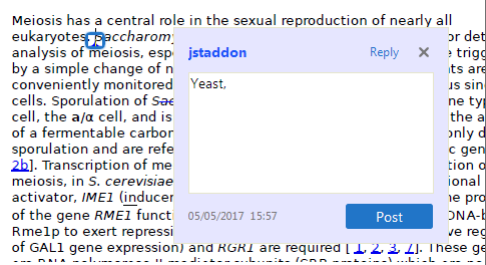
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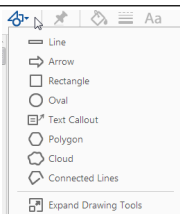
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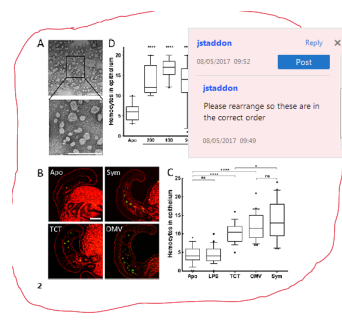


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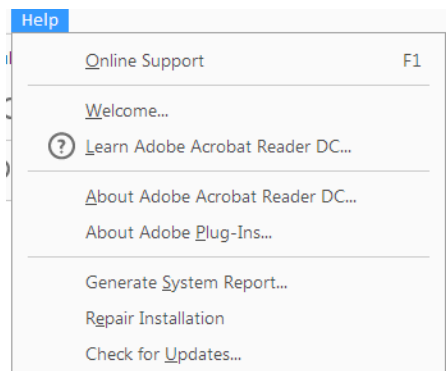
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Case Report

Recurrent massive pulmonary emboli in a critically ill patient with COVID-19

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Summary

We report the haematological management of a critically ill patient with COVID-19, with recurrent massive pulmonary emboli. A previous healthy, 56-year-old man presented to the emergency department with severe hypoxaemic respiratory failure due to suspected COVID-19. He required invasive mechanical ventilation and transfer to the intensive care unit for increasing ventilatory requirements and cardiovascular instability. A CT pulmonary angiogram demonstrated large bilateral pulmonary emboli with right heart strain, for which he received intravenous systemic thrombolysis followed by therapeutic weight-adjusted anticoagulation with low molecular weight heparin (dalteparin). Two weeks later, following an acute respiratory deterioration, a repeat CT pulmonary angiogram demonstrated a new saddle embolus with right heart strain requiring another regime of intravenous systemic thrombolysis. This occurred despite anti-Xa-guided therapeutic anticoagulation. The dose of therapeutic dalteparin was increased incrementally to an eventual dose of 12,500 units twice daily. A low threshold for radiological imaging should be considered in all COVID-19 patients with acute cardiorespiratory deterioration. Multidisciplinary team discussions highlighted aspects of balancing the risks of bleeding from anticoagulation vs. risk of death from pulmonary embolism. This report highlights the need for further research into the underlying mechanisms and optimal management of thrombotic complications in COVID-19.

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Introduction

Thrombotic complications, in particularly pulmonary emboli, are common in critically ill COVID-19 patients with a reported prevalence of 31–45% [1,2], despite the use of thromboprophylaxis. In the absence of high-quality data from randomised controlled trials, national guidelines now recommend escalated dose-intensity thromboprophylaxis protocols based on disease severity, clinical features and laboratory parameters, such as D-dimer [3]. The efficacy of increased anti-coagulant dosing must be balanced against the increased risk of bleeding, the background risk of which is approximately 3.5% in critically ill patients [4]. A multidisciplinary approach between critical care, haematology and radiology is essential for the management of these patients. We report a case of a critically ill patient with confirmed COVID-19 who initially presented with a massive pulmonary embolism. Despite initial thrombolysis and therapeutic anticoagulation, this patient went on to develop a second massive saddle pulmonary embolism.

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Report

A 56-year-old man presented to the emergency department with worsening dyspnoea and suspected COVID-19. His trachea was intubated for severe type one respiratory failure ($\text{PaO}_2/\text{FiO}_2$ ratio 7 kPa) and admitted to the intensive care unit (ICU).

On admission, he remained severely hypoxaemic with hypotension unresponsive to fluid resuscitation, and requiring vasopressor support. An electrocardiogram showed widespread ST-segment depression. Salient laboratory investigations included a D-dimer level of $8000 \mu\text{g}.\text{mL}^{-1}$ and troponin T of $3763 \text{ ng}.\text{mL}^{-1}$. Full blood count and coagulation profile were unremarkable. Admission thromboelastography demonstrated normal R time (7.4 min), alpha angle (68.7) and maximum amplitude (62.9 mm) with zero lysis at 30 min. A CT pulmonary angiogram (CTPA) showed bilateral large volume lobar and segmental pulmonary emboli with right ventricular strain (Fig. 1a,b). Transthoracic echocardiography showed right ventricular dilatation and systolic dysfunction, with flattening of the interventricular septum, consistent with right ventricular pressure and volume overload (Fig. 1c). Additionally, there were features suggestive of moderate to severe COVID-19 pneumonia. The Pulmonary Embolism Severity Index score was 152 points, which is classed as high risk and equates to a 30-day mortality rate between 10 and 24%.

The patient received intravenous (i.v) systemic thrombolysis with a 10 mg alteplase bolus followed by a 90 mg infusion over 2 h. Systemic, rather than catheter-directed thrombolysis, was chosen due to worsening haemodynamic instability, rising noradrenaline requirements and potential delay to accessing interventional radiology out of hours. The patient was then commenced on subcutaneous (s.c.) treatment dose dalteparin at a renal-adjusted dose of 12,500 units once daily for new acute kidney injury (serum creatinine $173 \mu\text{mol}.\text{L}^{-1}$). This was increased to a full weight-adjusted dose of 18,000 units once daily following 48 h of renal replacement therapy.

An interval CTPA 10 days later showed significant reduction in clot burden with reduction in right heart strain. However, 1 week later, the patient acutely deteriorated with worsening respiratory failure ($\text{PaO}_2/\text{FiO}_2$ ratio 11 kPa) and haemodynamic instability. A repeat CTPA showed a new saddle embolus and multiple bilateral emboli with multiple areas of pulmonary infarction with associated cavitation and evidence of increased right heart strain, (Fig. 1d). Anti-factor Xa levels were within therapeutic range immediately before these events. Following discussion with haematology and interventional radiology, a decision was made for further systemic thrombolysis. As before, the patient received a bolus of 10 mg alteplase i.v. followed by a 90 mg infusion over 2 h. The dose of s.c. LMWH was increased to 10,000 units dalteparin twice daily on haematological advice. A thrombophilia screen was not advised due to the likely confounding nature of his intercurrent illness. Lower limb Doppler showed a short segment of occlusive thrombus in the posterior tibial and medial gastrocnemius vein but no proximal thrombus.

Subsequent anti-factor Xa levels were subtherapeutic and his dalteparin was further increased to 12,500 units twice daily following haematology advice. A repeat CTPA 2 weeks later showed improved clot burden (Fig. 1g). To date, the patient has not experienced any bleeding complications. He remains an inpatient on the ICU.

Discussion

Venous thromboembolism in critical illness is not a new phenomenon. Even with widespread established use of both mechanical and pharmacological thromboprophylaxis, the mean incidence of venous thromboembolism has been shown to be between 2% and 40%, with associated ICU mortality rates ranging from 12.0% to 21.3% [5].

Published data suggest that critically ill patients with COVID-19 experience an increased burden of thrombotic complications with reported rates ranging from 25% to 45% [1,2,6]. In one study, one third of patients were diagnosed with a thrombotic complication despite being on therapeutic anticoagulation [2].

Low-quality observational data have reported a mortality benefit associated with heparin [6]. However, these studies have largely been single-centre, conducted in settings where routine thromboprophylaxis is not standard practice and are subject to immortal time bias. In addition, the optimal dose, route and timing of anticoagulation is still uncertain. Despite this, national UK guidelines now recommend escalated dose thromboprophylaxis given at an 'intermediate' dose, between that typical for prophylaxis and treatment [3]. Use of markers of coagulation, such as D-dimer, have been proposed to guide the clinical decision of when to escalate to intermediate dose thromboprophylaxis. Cui et al [7] found that a D-dimer of $> 3000 \text{ ng}.\text{mL}^{-1}$ had a sensitivity and specificity of 70% and 97%, respectively, for predicting thrombotic complications in a small, single-centre study. Thromboelastography may be a useful tool for guiding therapy in major haemorrhage but there are no published data

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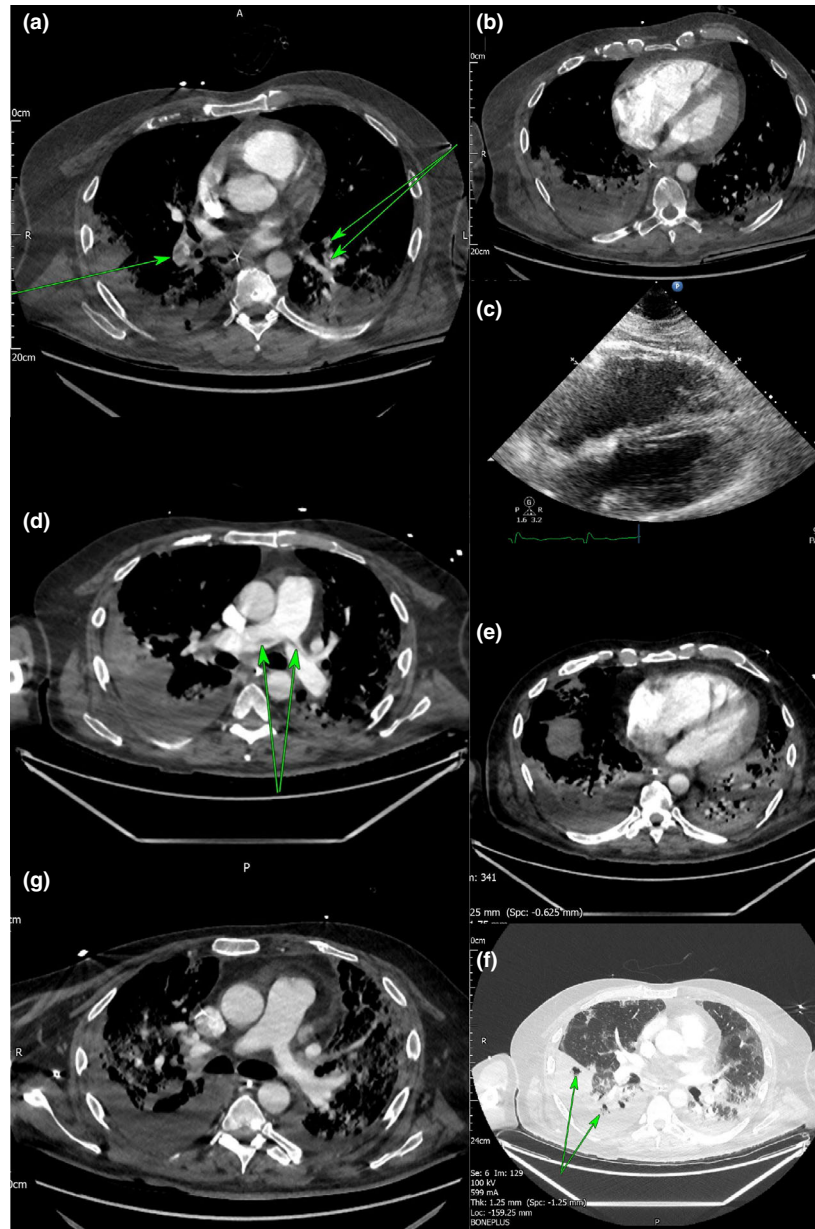


Figure 1 CT pulmonary angiogram on admission demonstrating: (a) bilateral segmental PE; and (b) right ventricular dilatation. Bed-side transthoracic echocardiography demonstrating (c) right ventricular dilatation and flattening of the intraventricular septum. Repeat CT pulmonary angiogram showing: (d) new saddle thrombus; (e) new right ventricular dilatation; and (f) improved clot burden following second episode of thrombolysis. The video URL is: https://youtu.be/Lfhj_bcT4gc

validating the use of thromboelastography to guide anticoagulation treatment in COVID-19. The admission thromboelastogram in our case was non-discriminatory.

Increased doses of anticoagulation must be weighed carefully against the risks of bleeding. These risks are not insubstantial in critically ill patients. Rates of gastrointestinal haemorrhage among ICU patients have been described as approximately 3.5% [4], with increasing bleeding risk and mortality in sicker patients and those with predisposing illness, such as liver or haematological disease. Our own experience has shown a bleeding rate of 12% in COVID-19 patients (unpublished data) and another study showed a major bleeding rate of 7.5% in intubated COVID-19 patients [8].

These data highlight the need to balance the risks of bleeding with the risks of thrombosis. With observational data from several studies demonstrating a marked pro-thrombotic state in COVID-19 [1,2,7,8], this is now a recurring theme in the management of these patients, as highlighted by our case – where the patient underwent two separate episodes of systemic thrombolysis. This complexity of clinical situation is likely to be best managed using a multidisciplinary approach with input from specialties outside of intensive care. Haematologists provided input throughout this patient's case with respect to optimal anticoagulation and monitoring, including the use of anti-Xa levels. Low molecular weight heparin was used at doses outside of our local Trust guidelines based on this advice. The use of intravenous unfractionated heparin was considered, but dismissed, as unfractionated heparin has a short half-life, requires frequent monitoring (challenging at a time of reduced nurse to patient ratios) and has been shown to deliver sub-optimal anticoagulation [9]. Interventional radiology expertise was invaluable in deciding how and whether to provide thrombolysis, together with interpretation of the serial cross-sectional imaging regarding clot burden and amenability to catheter-directed thrombolysis.

This case report serves to highlight that the inflammatory response associated with the COVID-19 syndrome may confer increased thrombotic risk and that increased anticoagulation may not completely mitigate against this. There may be a need to deviate and/or adapt existing anticoagulation guidelines as has been described recently in a case of airway management in COVID-19 [10]. There is a need for further research into the underlying mechanisms of thrombosis associated with COVID-19 and for randomised controlled trials to better understand the risk-benefit ratio of different anticoagulation strategies.

Acknowledgements

Published with the written consent of the patient's nominated next of kin. We would like to thank S Shilston for her assistance in providing and interpreting the relevant radiology images. AS is currently being supported by an NIHR Doctoral Research Fellowship (NIHR-DRF-2017-10-094). No other external funding or competing interests declared.

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