





CASE BASED DISCUSSIONS

Coexistent COVID-19 pneumonia and pulmonary embolism: challenges in identifying dual pathology

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CASE

In early March 2020, a 53-year-old man was admitted to King's College Hospital (KCH). He presented with a 2-week history of a dry cough, followed by fevers. He had a long flight 9 weeks prior to admission. His presentation to the emergency department was prompted by feeling increasingly breathless; his cough was occasionally productive of yellow sputum with streaks of haemoptysis. He had no medical history. His temperature was 38°C with peripheral oxygen saturation level of 92% on room air, respiratory rate was 28 breaths per minute but he was haemodynamically stable with blood pressure 128/75 mm Hg and heart rate 98 beats per minute.

A chest X-ray on arrival showed bilateral infiltrates with denser consolidation in the right lower and upper zone. An arterial blood gas showed type 1 respiratory failure with pH 7.52, PaCO₂ 3.87 kPa, PaO₂ 8.45 kPa and lymphopenia $0.86 \times 10^9/L$. ECG demonstrated sinus rhythm.

The patient was suspected to have viral pneumonia—likely COVID-19. He was given oxygen to target saturations 94%–98%, covered for bacterial infection as per local community-acquired pneumonia protocol and given venous thromboembolism (VTE) prophylaxis in the form of enoxaparin 40 mg once daily. Viral RT-PCR (reverse transcription polymerase chain reaction) for COVID-19 from naso-oropharyngeal and oropharyngeal swabs on both day 1 and day 2 of admission were negative. Urinary pneumococcal and legionella antigens were also negative. His D dimer was 2560 ng/mL (normal <500 ng/mL) and serial troponin Ts were 3 and 7 ng/L (normal <14 ng/L).

Given his ongoing oxygen requirement and negative viral swab, a CTPA (computed tomography pulmonary angiogram) was performed. This showed acute bilateral pulmonary emboli (PE) with evidence of pulmonary infarcts and background changes suggestive of infective aetiology or acute respiratory distress syndrome (ARDS). A third swab for viral RT-PCR on day 3 confirmed COVID-19 infection. The patient was switched to oral edoxaban after 5 days of treatment dose enoxaparin and was discharged off oxygen 5 days after presentation.

Since this early case of COVID-19 in the UK, in our practice, based in London, we have observed numerous PE events in patients with COVID-19 infection. We found this striking given the difficulty in identifying concomitant PE in this patient group based on the clinical history and serological tests.

We have summarised the demographics and clinical findings of the first 10 patients admitted to KCH with COVID-19 pneumonia and coexistent PE. The patient summarised above is case G.

The demographics, clinical and imaging findings of 10 patients identified with PE and COVID-19 infection in March 2020 presenting to our institution are detailed in [table 1](#). Sample images are shown in [figure 1](#). All scans were retrospectively reviewed by an experienced chest radiologist.

DISCUSSION

Though the relationship between SARS-CoV2 infection and predisposition to pulmonary embolism is poorly described, there is a strong association between VTE and viral pneumonia. In a critically ill ARDS cohort with Influenza A H1N1 infection, the incidence of pulmonary embolus was 29% compared with 8.5% in those without H1N1.¹ These data suggest a mechanism of clot formation beyond critical illness that may be related to viral damage.

Coagulopathy is a common feature of severe COVID-19 infection, the most striking feature an elevated level of D dimer, a fibrin degradation product. Unlike disseminated intravascular coagulation, patients are not typically thrombocytopenic nor have evidence of severe clotting time derangement; this would suggest a process of localised thrombin generation and fibrinolysis. In part, this may be secondary to the over-expression of the cytokine interleukin-6 (IL-6) which is produced by multiple cell types, primarily immune cells but also non-immune tissue such as vascular endothelium. It has both pro and anti-inflammatory properties and plays a key role in the immune response to viral pneumonia. In H1N1 infection, IL-6 expression may be advantageous by protecting neutrophils from virus-induced death in the lung and promoting neutrophil-mediated viral clearance.² Conversely, in COVID-19, IL-6 appears central to an overzealous immune response with levels nearly threefold higher in patients with COVID-19 infection complicated by ARDS vs non-complicated disease.³ At the time of writing, it is suggested that an IL-6-mediated pulmonary hyperinflammatory process may extend into the adjacent microcirculation resulting in severe local vascular dysfunction including micro-thrombosis and haemorrhage with a resultant lung-centric pulmonary intravascular coagulopathy.⁴



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Table 1 Summary of 10 cases of COVID-19 pneumonia with pulmonary embolism identified on CT angiography

Case	Age	Sex	Presenting history	Chest radiograph	Relevant comorbid conditions	D-dimer (ng/ml)	Troponin (ng/L)	Indication for CTPA	Highest level of PE on CTPA	Right heart strain on CT	CT evidence of infarcts	Management of VTE	Ventilatory support	Evidence of DVT on USS
A	56	Male	7 days cough, fever	Bilateral infiltrates	T2DM	>8000	8	Chest pain	Subsegmental	No	No	DOAC	High flow oxygen	No
B	64	Male	9 days cough, SOB	Bilateral infiltrates	HTN, CKD	>8000	–	Syncopal episode	Main	Yes	Yes	LMWH	High flow oxygen	No
C	57	Female	15 days fever, cough SOB	Clear	–	>8000	309	>3 weeks of SOB	Main	Yes	Yes	Thrombolysis	High flow oxygen	No
D	71	Male	7 days lethargy, fever, cough	Bilateral infiltrates	–	>8000	406	Persistent high P/F ratio	Lobar	Yes	Yes	LMWH	High flow oxygen	No
E	66	Male	9 days cough, fever, SOB	Right upper lobe and left lower zone consolidation	–	4990	13	Persistent high P/F ratio	Segmental	Yes	No	LMWH	High flow oxygen	Yes
F	62	Male	10 days SOB, diarrhoea	Bilateral infiltrates	–	>8000	37	Chest pain	Segmental	Yes	No	LMWH	Intubated and Ventilated	No
G	53	Male	13 days cough, fever, SOB	Bilateral consolidative change	–	2560	7	Pleuritic chest pain, Persistent high P/F ratio	Lobar	Yes	Yes	DOAC	High flow oxygen	No
H	71	Male	13 days fever, coryza	Unilateral linear atelectasis	T2DM	2490	177	Syncopal episode	Main	Yes	No	LMWH	High flow oxygen	No
I	63	Male	7 days SOB, cough, fever	Bilateral infiltrates	T2DM, HTN, IHD	>8000	21	Clinical evidence of DVT, raised D-dimer	Main	Yes	No	LMWH	High flow oxygen	Yes
J	75	Female	Inpatient - 2 days of SOB and increasing oxygen requirement	Bilateral infiltrates	Bladder cancer with ureteric obstruction, COPD	>8000	74	Staging CT scan	Subsegmental	No	No	Heparin infusion	High flow oxygen	Yes

DOAC, direct oral anticoagulant; DVT, deep vein thrombosis

; HTN, hypertension; IHD, ischaemic heart disease; LMWH, low-molecular-weight heparin; P/F ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen; SOB, shortness of breath; T2DM, type 2 diabetes; USS, ultrasound.

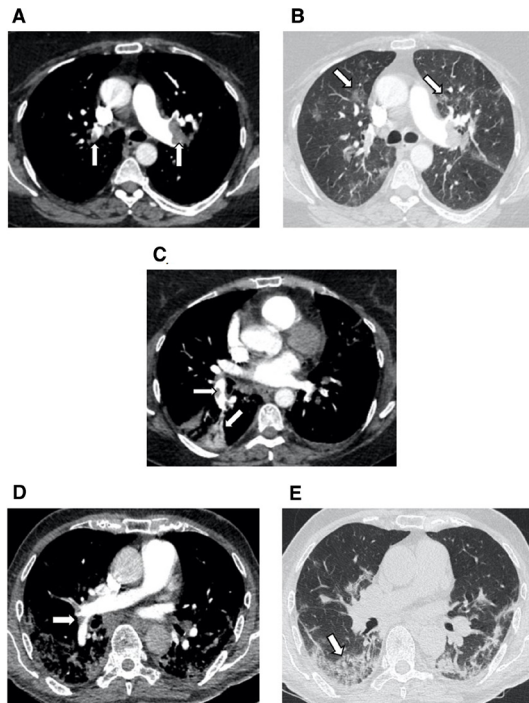


Figure 1 (A-C) show sample axial CT images of a CTPA in patient C with moderate COVID-19 pneumonia as demonstrated by bilateral round peripheral and bronchocentric ground glass opacities (arrowed). There are extensive bilateral main and lobar pulmonary emboli (PEs) (arrowed) with a wedge shaped infarct in the right lower lobe (arrowed). (D,E) show axial CT images of CTPA (computed tomography pulmonary angiogram) in patient D with severe COVID-19 pneumonia as demonstrated by peripheral ground glass opacification and consolidation (arrowed) with perilobular pattern (arrow). There are segmental PEs (arrowed).

This notion is supported by examination of pathology specimens from COVID-19-infected patients which also demonstrate evidence of pulmonary vascular changes with vessel wall thickening, lumen stenosis, occlusion and microthrombosis formation.⁵ However, it is unclear if a similar process results in ‘in situ’ pulmonary embolus formation. In clinical practice, retrospective data from China suggest reduced mortality in patients treated with low molecular weight heparin⁶ but this is yet to be prospectively evaluated.

We have identified 10 cases of coexisting PE and COVID-19; in general, these were identified with symptoms highly suggestive of PE and a very elevated D dimer. It is likely that there are

many more cases of PE that have been missed due to the similarities in presentation between PE and COVID-19 pneumonia. These cases highlight a diagnostic challenge in severe COVID-19 infection, and it is not yet clear whether associated PE affects outcome in these patients. Patients typically present to hospital with an elevated alveolar-arterial oxygen gradient and bilateral infiltrates on chest radiography. D-dimer levels are measured for prognostication, but due to the limited specificity of the assay, it is easy to overlook concomitant VTE in this patient group.

Until large prospectively collected data are available, based on our experiences to date, we suggest a lower threshold to perform CT angiography in patients COVID-19 pneumonia, particularly in those with a prolonged history of illness and immobility before admission, grossly elevated D-dimer, lack of improvement or clinical deterioration with increasing oxygen requirement.

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