Case report

Catheter-directed thrombolysis to treat acute pulmonary thrombosis in a patient with COVID-19 pneumonia

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SUMMARY

We describe a case of a patient who presented to the emergency department with severe shortness of breath and was diagnosed with mild COVID-19 pneumonia and concomitant intermediate-high risk saddle pulmonary thromboembolism. Additionally, the patient had sustained a significant head injury 2 days prior due to a syncopal episode. The patient was treated successfully with catheter-directed thrombolysis (CDT). The case highlights the importance of considering thromboembolic complications in COVID-19 infection, independent of the severity of the associated pneumonia. The case also demonstrates the potential benefit of CDT in treating COVID-19-related thromboembolism.

BACKGROUND

In December 2019, the first reports of a novel coronavirus infection emerged from Wuhan, China. In the following 4 months, the disease, subsequently known as COVID-19, has spread throughout the world. As this is a new disease, there is little known about its effects and complications.

There is a growing body of evidence that the infection is associated with a prothrombotic state, with a variety of thrombotic and embolic complications seen, potentially affecting any of the organ systems. A complication with high morbidity and mortality is pulmonary thromboembolism (PT). Studies looking at the incidence of PT in patients admitted to intensive care unit (ICU) with severe COVID-19 pneumonia have found rates between 25% and 43% and the presence of PT likely leads to worse outcome (table 1).[1–4]

A study by Middeldorp *et al*[5] has found a cumulative incidence of 3% in non-ICU hospitalised patients despite thromboprophylaxis. There has been less investigation into the incidence of PT among patients presenting to the emergency department not immediately requiring critical care support and only few published reports of PT in mild COVID-19 pneumonia cases not otherwise requiring hospital admission. A high index of suspicion should be maintained that PT may contribute to the clinical deterioration of patients with COVID-19 pneumonia.

Pulmonary thromboembolic disease is risk stratified as high risk (massive), intermediate-high/intermediate-low risk (submassive) and low risk (minor) based on degree of haemodynamic compromise and right heart dysfunction (table 2).

High risk and intermediate-high risk cases have significant associated mortality (table 3), and thrombolysis is advocated for selected cases to reduce the right ventricular (RV) afterload and improve pulmonary perfusion.

Systemic thrombolysis carries a risk of haemorrhage,[6] which is mitigated by the use of catheter-directed thrombolysis (CDT) that allows targeted delivery and lower doses of thrombolytic agent use.[7 8]

CASE PRESENTATION

A 64-year-old woman who was previously well and living independently presented to her local hospital with two episodes of syncope. She had felt generally unwell with some breathlessness for the preceding 2 weeks, but no cough or fever. One of the syncopal episodes was while she was working at home from her desk and she sustained a head injury that resulted in a significant periorbital haematoma. She complained of shortness of breath, dizziness, chest pain and diplopia. Her medical history included asthma, hypothyroidism, depression and an unprovoked deep vein thrombosis 10 years previously.

On examination, she was found to have crackles at the right base and a large periorbital haematoma. On presentation, her oxygen saturations were 96% on room air, but while in hospital acutely desaturated to 76%. Therefore, she underwent a CT pulmonary angiogram (CTPA).

Investigations

- Chest radiograph on admission demonstrated left-sided mid-lower zone subpleural airspace consolidation and minor right lower zone subpleural subtle airspace consolidation (figure 1).
- The D-dimer was 5.43 mg/L on admission, peaked at 78.37 and 0.23 mg/L on discharge (normal range 0–0.55 mg/L).

Table 1 VTE incidence in COVID-19 patients in ICU[1–4]

Study	No of patients	Thrombosis rates
Klok *et al*[1]	184 patients 3 centres	Cumulative 31%
Cui *et al*[2]	81 patients 1 centre	25%
Helms *et al*[3]	150 patients 4 centres	43%
Thomas *et al*[4]	63 patients 1 centre	29%

ICU, intensive care unit; VTE, venous thromboembolism.

Table 2 Risk stratification of pulmonary embolism[1]

Early mortality risk		Indicators of risk: Haemodynamic instability	Clinical parameters of PE severity and/or comorbidity	RV dysfunction of TTE or CTPA	Elevated cardiac troponin levels
High		+	(+)	+	(+)
Intermediate	Intermediate-high	–	+	+	+
	Intermediate-low	–	+	One or neither +	
Low		–	–	–	–

Colours provides a traffic light system to draw attention to the severity of the condition.
CTPA, CT pulmonary angiogram; PE, pulmonary embolism; RV, right ventricular ; TTE, Trans thoracic echocardiography.

- Her C reactive protein was 8 mg/L (0–4), ferritin 414 mcg/L (13–150), and Clauss fibrinogen 3.8 g/L (1.7–3.9).
- COVID-19 PCR test taken on admission gave positive result on day 1 after admission.
- The B-type natriuretic peptide (NT-proBNP) was 1527 ng/L (<150 ng/L) and troponin T 181 ng/L (0–13).
- CTPA showed extensive bilateral lobar, segmental and subsegmental pulmonary emboli with a large saddle embolus, with dilatation of the RV (RV:left ventricle ratio=2.5) (figures 2–4). In addition, there was bilateral lower lobe predominant subpleural reticulation associated with scattered ground glass opacities (figures 5 and 6). Findings were in keeping with mild COVID-19 pneumonitis.
- CT head did not reveal intracranial haemorrhage or retro-orbital pathology.
- Bedside echocardiogram confirmed right heart strain.
- Bilateral lower limb Doppler scans did not show any deep vein thrombosis.

Differential diagnosis

The patient was initially treated for exacerbation of asthma. The CTPA demonstrated saddle PT and features of COVID-19 pneumonia, later confirmed by PCR result.

Treatment

The patient was initially managed with high-flow oxygen and administration of 15 000 units of dalteparin. PT in this case was stratified as 'intermediate-high risk'. Owing to clinical deterioration in symptoms resulting in increased oxygen requirement, a multidisciplinary team decision was made to proceed with CDT.

Infusion catheters were placed in both pulmonary arteries and ultrasound assisted CDT (EkoSonic Endovascular System, Boston Scientific) with alteplase was commenced (figure 7). All members of the IR team wore appropriate personal protective equipment, and the patient was nursed on the COVID-19 ICU. After 24 hours, the infusions were stopped and the catheters removed. The total administered dose of alteplase was 40 mg. The patient was then commenced on split treatment dose dalteparin and converted to apixaban prior to discharge.

Table 3 Percentage mortality from pulmonary embolism[1–4]

Risk assignment	% Patients	% Mortality
Massive (high)	5	>50
Submassive (intermediate-high)	10	21–29
Submassive (intermediate-low)	15	3–15
Minor (low)	45–70	1.5

OUTCOME AND FOLLOW-UP

The patient experienced minor complications of thrombolysis with two episodes of epistaxis and a single episode of melaena, which were self-limiting.

The patient had a very good clinical response to thrombolysis and was weaned off oxygen support within 24 hours. She was discharged home 6 days after the CDT procedure once she was able to mobilise independently without oxygen support.

Telephone consultation was conducted 4 weeks later. The patient describes her breathlessness as much better and was doing well at home.

Discussion

Knowledge surrounding COVID-19 is continuously changing as this is a new disease. Evidence of association between COVID-19 and a prothrombotic state has recently emerged. There are a number of proposed mechanisms to explain this. One hypothesis is that acute lung injury leads to a profound inflammatory reaction with cytokine storm, which causes endothelial cell activation and apoptosis and ultimately activation of the coagulation cascade.[9] Parallel to this, hypoxia has been demonstrated to induce a prothrombotic state.[10 11]

Increased incidence of pulmonary embolism appears to be part of the prothrombotic spectrum associated with COVID-19 as demonstrated by recent reports. The majority of published cases describe pulmonary embolism in the context of severe COVID-19 pneumonia requiring hospitalisation or ICU admission. Two reports have described patients with mild symptoms who presented with low risk pulmonary emboli successfully treated with anticoagulation alone.[12 13] Segmental or

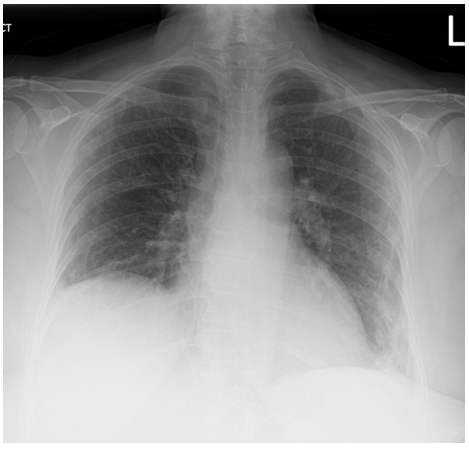

Figure 1 Anteroposterior erect chest X-ray shows left mid-lower zone subpleural airspace consolidation and minor right lower zone subpleural subtle airspace consolidation.

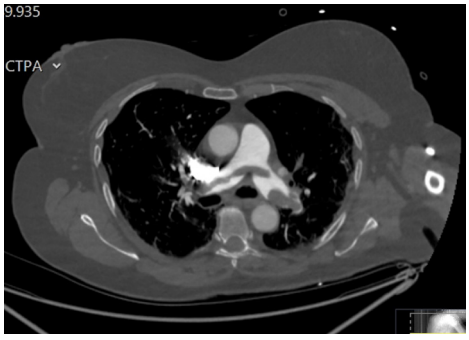

Figure 2 Axial image from the CT pulmonary angiogram (CTPA) demonstrates bilateral proximal pulmonary emboli and large saddle embolus.

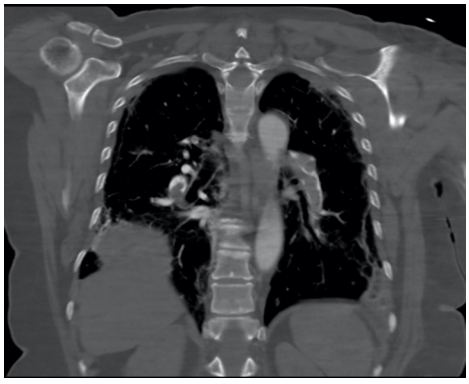

Figure 3 Coronal reconstruction from the CT pulmonary angiogram demonstrates bilateral proximal pulmonary emboli.

subsegmental PT is likely caused by localised immunothrombosis rather than pulmonary emboli as few patients are found to have concurrent deep vein thrombosis. Hence, it is conceivable that the localised inflammation is leading to pulmonary thrombosis as occurs in cases of acute respiratory distress syndrome.[14]

The interesting aspect of our case is that the patient presented had only mild COVID-19 pneumonia, and her acute severe clinical deterioration was most likely due to her intermediate-high risk saddle pulmonary thrombosis causing RV dysfunction than the mild pneumonitis. Early identification of PT allowed us to safely and effectively manage her with CDT. Only one case from Northern France has been previously published presenting a 45-year-old woman with massive pulmonary embolism and

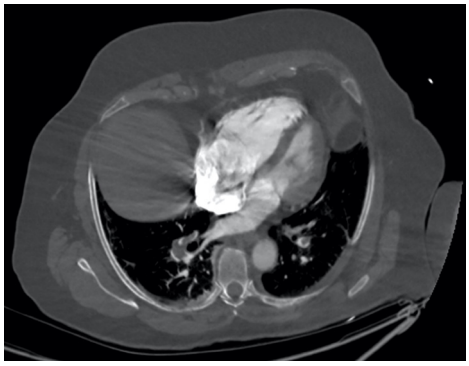

Figure 4 Axial image taken from CT pulmonary angiogram demonstrates dilatation of the right ventricle and mild interventricular septal bowing, in keeping with right heart strain.

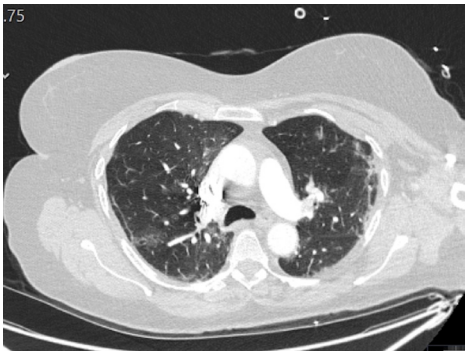

Figure 5 Axial lung window images from CT pulmonary angiogram demonstrates bilateral subpleural reticulation, associated with bilateral scattered ground glass opacities with a mainly interlobular and subpleural distribution, predominant on the left.

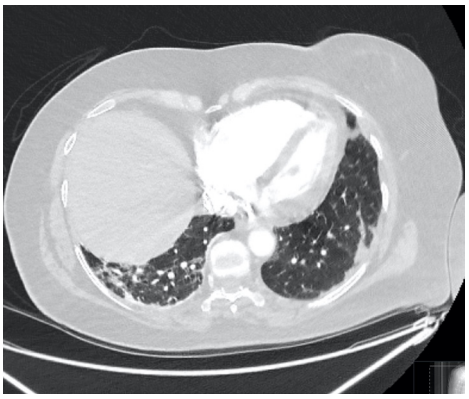

Figure 6 Axial lung window images from CT pulmonary angiogram demonstrates slightly denser left-sided basal subpleural consolidation.

only mild COVID-19 symptoms, who was treated with surgical embolectomy but did not recover.[15] The case presented highlights the need to remain vigilant for possible PT in patients with COVID-19 infection who clinically deteriorate, independently from the extension of the associated pneumonitis. The presence of RV dysfunction that may be shown on an echocardiogram should raise the possibility of pulmonary thrombosis as the possible underlying cause. Although there is some data on the incidence of thrombosis in patients with COVID-19, there is little data available with respect to bleeding complications. Post-mortem series have commented on the presence of pulmonary haemorrhage. CDT was chosen over systemic thrombolysis in this case due to the presence of the large periorbital haematoma

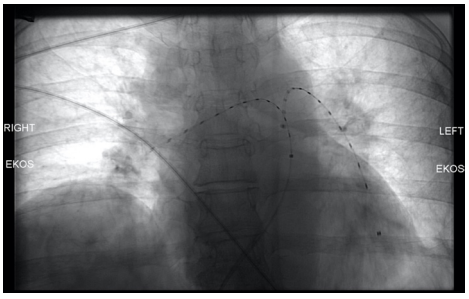

Figure 7 Fluoroscopic image demonstrates placement of the EkoSonic catheters in the pulmonary arteries.

Patient's perspective

I self-isolated on the 23rd March and began working from home. Prior to being admitted to the local hospital, my breathing had deteriorated and my chest felt tight. Being an asthma sufferer I contacted my GP on the 30th March, who prescribed steroids and antibiotics. On completing the course I felt much better but developed a pain in the left side of my chest that I thought was a muscle strain from coughing.

On the 13th April I was working at my computer when I became disoriented and passed out. On coming to, I contacted 111 who sent out medical support. I had hit the left side of my face on the table and suffered a lump to my head and jaw, and overnight developed a black eye. I was assessed by the ambulance crew but as I was feeling better I declined to go to hospital. During the night I went to the bathroom and on returning to bed became disoriented and was violently sick, my vision had also become blurred. I called my daughter who called 111 who promptly sent an ambulance.

On arrival at my local hospital on 14th April I struggled with the overhead lighting and then had various scans and a chest x-ray. I was moved to a ward feeling much better. I went to the bathroom and again passed out, I was brought round and moved to a side ward, not remembering very much. Doctors came to my room and informed me that my condition required specialist treatment and that I was to be transferred to a specialist hospital immediately. On arrival I was taken to the high dependency unit and further tests and scans were done. Doctors came to my room and explained that I had blood clots on my lungs that had caused stress on my heart. They considered that the best procedure to perform was Catheter Directed Thrombolysis, although it carried serious risks and could result in loss of life. I knew that the blood clots could travel and cause death and considered that if it would save my life I should allow them to go ahead. Signing the consent form was very hard.

After the procedure I had to lie still for 12 hours while the medication was put into my system, it was them decided to increase the time for a further 12 hours until the leads that were thread from my groin to my lungs were removed. At this time I was told to keep as still as possible to avoid dislodging the wires. I remember having a couple of nosebleeds which were unpleasant as I was flat, but they did stop of their own accord once pressure had been applied to the bridge of my nose. I remember asking for reassurance from the medical staff that I was not going to die, and was relieved to see the following day.

Over the course of the next 24 hours my breathing had improved greatly and it was a surprise to me that my breathing had been so bad. I went from feeling like I couldn't breathe in fully to being able to take deep breaths with no pain and feeling I was filling my lungs to capacity. I was transferred from HDU to Somerset ward where I continued to improve and was discharged on the 22nd April.

Since I returned from the hospital I have continued to live alone, I have my shopping delivered by family and my GP has been in contact. I have been able to manage day to day and been making a concerted effort to spend some time taking gentle exercise walking up and down the road I live on, as spending time in the garden ensuring to wear a sun hat and keep hydrated. I have been taking my medication as prescribed and have not felt the need to take any additional painkillers on a regular basis.

Learning points

- COVID-19 infection can be complicated by pulmonary thromboembolism even when the extent of the lung parenchymal infection is mild.
- In cases where the degree of breathlessness or hypoxia is disproportionate to the severity of lung changes on chest radiograph, pulmonary thromboembolism should be suspected and physicians should have a low threshold for performing CT pulmonary angiography.
- Management of pulmonary thromboembolism with catheter-directed thrombolysis in patients with COVID-19 infection is a potentially safe and effective treatment, and further trials should be conducted.

and also to minimise the risk of pulmonary haemorrhage, given the changes suggestive of COVID-19 pneumonia.

Identifying pulmonary thrombosis in patients with COVID-19 infection can be challenging on clinical and laboratory parameters only. Specifically, D-dimer is often raised in COVID-19 pneumonia independently from the presence of PE,[16 17] limiting the usefulness of serum D-dimer as a screening test. CT pulmonary angiography is the optimum imaging modality for the diagnosis of PT and clinicians should have a low threshold for obtaining this especially when the degree of breathlessness or hypoxia is out of keeping with the severity of parenchymal changes seen on the chest radiograph.

Guidance on thrombophylaxis in hospitalised patients with confirmed COVID-19 infection[18] has been published; however, guidelines for management of thrombosis in the context of COVID-19 are not yet in place. Theoretically, there is a risk of pulmonary haemorrhage with systemic thrombolysis due to the profoundly inflamed lung parenchyma. We hypothesise this risk can be reduced with the use of CDT, as in our case.

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