Case report

Acute cerebrovascular event in a COVID-19 positive patient immediately after commencing non-invasive ventilation

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SUMMARY
A 71-year-old man presented to the emergency department (ED) with low oxygen saturations and symptoms consistent with COVID-19 infection. Apart from a small left-sided ischaemic stroke 10 years prior with very minor residual deficit, he had been well and in full-time employment until development of symptoms. Within minutes of commencing non-invasive ventilation (NIV) in the ED, he developed a complete left-sided paralysis and hemineglect. This case highlights the significance of the prothrombotic complications associated with COVID-19 infection. It also raises the question whether pressure changes upon commencing NIV could lead to clot migration.

BACKGROUND
SARS-CoV-2 was first identified in Wuhan, China in December 2019 and gives rise to a clinical syndrome known as COVID-19,1 2 manifested mainly by viral respiratory symptoms, but also with a vast range of other clinical manifestations, the extent of which is still emerging.3 Guidance on the management of COVID-19 respiratory failure has included the use of non-invasive ventilation (NIV) as promoted by the WHO, but this has been a controversial issue, and practice varies between different countries and health systems.4 5

Recently, infection with SARS-CoV-2 has also been linked to haemostatic abnormalities such as thrombotic events and disseminated intravascular coagulation.7 The majority of thrombotic events described in association with COVID-19 are pulmonary embolisms, with very limited literature on the occurrence of other thrombotic events such as cerebrovascular accidents (CVA). Previous reports during the SARS epidemic in 2003, however, found an association between the occurrence of CVA and the SARS virus.8

Here, we describe a case of SARS-CoV-2 infection which developed a multitude of prothrombotic events, starting with a stroke within minutes of starting NIV in the form of continuous positive airway pressure (CPAP), highlighting the severity of the prothrombotic risks associated with COVID-19.

CASE PRESENTATION
A 71-year-old man brought by ambulance to the emergency department (ED) during the peak of the COVID-19 pandemic in the UK in April 2020 with shortness of breath and low oxygen saturations of 50% on room air measured by pulse oximetry. He had a 3-week history of a dry cough and felt increased shortness of breath over the week prior to his admission with an acute exacerbation on the day of his admission. Prior to the ambulance service attending, he mobilised with difficulty due to shortness of breath but was able to walk and use all his limbs.

There was no history of fever, chest pain, calf tenderness or peripheral oedema.

His medical history included essential hypertension, hypercholesterolaemia and a left-sided ischaemic stroke 10 years prior, for which he had had a left-sided endarterectomy at the time and was left with minor residual weakness in the right hand only. His daily medications were once daily doses of amlodipine (5 mg), losartan (10 mg), simvastatin (20 mg) and clopidogrel (75 mg) which he reportedly was compliant to. He was functionally well, independent in all activities of daily life and was working full time in a manual job.

On examination, he was acutely short of breath with a high respiratory rate of 44 breaths/min, tachycardic at 120 beats/min and a blood pressure of 130/80 mm Hg. He was alert and orientated, able to answer questions and follow commands appropriately. There were widespread crackles bilaterally on chest auscultation. He was moving all limbs and managed to transfer independently from the ambulance stretcher to the hospital trolley.

Initial arterial blood gas (ABG) on 15 L/min oxygen delivered through a non-rebreathing mask showed type-1 respiratory failure with severe hypoxaemia with an oxygen saturation of 88% at 15 L/min oxygen.

Figure 1 Portable chest X-ray taken at admission showing severe bilateral pulmonary infiltrates consistent with COVID-19 infection.
respiratory acidosis. A bedside 12-zone lung ultrasound showed B-lines and interrupted pleura in all lung zones, absence of a pneumothorax and a grossly normal echocardiogram. He was commenced on CPAP delivered with a BiTrac SE Select full face mask size M (Pulmodyne, Indianapolis, Indiana, USA). Within 5 min of initiation of therapy, he was suddenly noted to start losing seal on the left side of the face mask. On re-examination, he had acquired a new total left-sided paralysis, left hemineglect and slurred speech. Decision was made to intubate for transfer to CT in view of the ongoing need for an aerosolising procedure (NIV) in a suspected COVID-19 positive patient.

INVESTIGATIONS
The throat swab PCR test for SARS-CoV-2 infection was positive. Blood results showed raised inflammatory markers with white cell count $12.3 \times 10^9$, neutrophils $10.6 \times 10^9$, lymphocytes $0.9 \times 10^9$ and CRP (C-reactive protein) $176 \text{mg/L}$. Liver function was deranged with ALT (alanine transaminase) $111 \text{units/L}$ and ALP (alkaline phosphatase) $235 \text{units/L}$. Renal profile and electrolytes included urea $8 \text{mmol/L}$, creatinine $47 \text{µmol/L}$, sodium $134 \text{mmol/L}$, potassium $4.2 \text{mmol/L}$. Ferritin was $10576 \text{µg/L}$, troponin $243 \text{ng/L}$ and D-dimer $9627 \text{µg/L}$. ABG analysis on 15L/min oxygen delivered via non-rebreathing mask showed a pH 7.18, $\text{PO}_2 8\text{kPa}$, $\text{Pco}_2 3.5 \text{kPa}$, lactate $2.9 \text{mmol/L}$, bicarbonate $22 \text{mEq/L}$ and base excess $6 \text{mmol/L}$.

A chest radiograph taken at the time of admission showed severe bilateral pulmonary infiltrates consistent with COVID-19 pneumonia (figure 1).

Initial CT scan of head was reported as not showing any acute signs of stroke. However, a subsequent CT scan of the head performed 40 hours post initial presentation showed extensive ischaemia in the right middle cerebral artery and posterior cerebral artery territories with haemorrhagic transformation and a small cerebellar infarct (figure 2). A further head CT 11 days post admission showed further evolution of the infarct.

CT angiogram of the aorta and carotid arteries 3 days after admission demonstrated significant calcification within both internal carotid arteries, but with less than 50% stenosis. CT pulmonary angiogram showed a subsegmental pulmonary embolism in the right upper lobe, as well as ground-glass opacification and areas of peripheral consolidation in keeping with COVID-19 pneumonia.

Figure 2 Sequential head CT scans of the same patient taken at different time points. (A) Scan performed 1 hour after symptom onset (showing no acute intracranial abnormality and (B) scan performed 40 hours after symptom onset showing infarction within the right PCA and MCA territories. MCA, middle cerebral artery; PCA, posterior cerebral artery.

TREATMENT
After ruling out a pneumothorax using ultrasound, the patient was immediately commenced on CPAP set to positive end-expiratory pressure of 10 mm Hg delivering 100% oxygen. Decision was made to intubate for transfer to CT in view of ongoing need for aerosolising procedure (NIV) in a likely SARS-CoV-2 positive patient. Following discussion with the stroke team at the primary stroke centre, the decision was made to thrombolysate locally in view of the likely COVID-19 infection. Thrombolysis was performed with an initial dose of 7 mg alteplase, followed by an infusion of 60 mg alteplase over 1 hour. Blood pressure was monitored to ensure it did not exceed a systolic value of 180 mm Hg. Following admission to the ITU (intensive treatment unit), the patient was commenced on an anticoagulant thromboprophylaxis dose of 40 mg enoxaparin, administered subcutaneously once daily.

OUTCOME AND FOLLOW-UP
The patient was transferred to the ITU for post-thrombolysis care. A multidisciplinary team meeting was held and the patient’s relatives were updated on the patient’s likely poor prognosis. Sedation holds on the ITU were unsuccessful. Unfortunately, the patient continued to deteriorate and died 7 days following his admission to the ITU.

DISCUSSION
COVID-19 is the clinical manifestation of SARS-CoV-2 infection and can present with a multitude of symptoms. These most commonly include a dry cough and fever frequently accompanied by anosmia, but the clinical presentation can also be atypical with mainly gastrointestinal, cardiovascular or neurological complaints, such as accounts of patients presenting with acute stroke, testing positive for SARS-CoV-2 infection. Infection with SARS-CoV-2 has been associated with a coagulopathic profile. Over one-third of patients admitted to ITU with COVID-19 have been found to develop thrombotic events despite thromboprophylaxis. Most of the available evidence describes pulmonary emboli as the main thrombotic events. The literature on CVA associated with COVID-19 is still sparse, but they appear to represent up 3.7% of the thrombotic complications in ITU patients. A recent case series published during writing of this case has reported of six COVID-19 patients that developed strokes. All patients had prior vascular risk factors and features of severe COVID-19 pneumonia and had a poor outcome.

Contributory factors to the prothrombotic nature of the COVID-19 phenotype may include pre-morbid risk factors, the general effects of severe illness and hypoxia, but also the severe inflammatory response seen with SARS-CoV-2 infection, and the multitude of derangement of various haematological laboratory parameters. These include markedly increased D-dimer, prolonged prothrombin time and elevated inflammatory markers such as interleukin-6, all contributing to a procoagulant state with excessive platelet activation, endothelial dysfunction and stasis.

Patients with previous cardiovascular disease appear at increased risk for adverse outcomes, but even without prior disease, severe COVID-19 infection may lead to cardiovascular complications.

Guidance published by the WHO and the UK National Health Service recommends NIV as treatment modality for respiratory failure in COVID-19 pneumonia particularly as an early application and bridge to invasive mechanical ventilation. Other
guidelines caution against routine use of NIV in COVID-19 respiratory failure, however, quoting the risks for a high failure rate, delayed intubation and increased risk of aerosolisation through poor fitting masks.\(^6\)

The striking feature in the case presented was the development of stroke symptoms within minutes of starting CPAP. The timing of stroke symptoms so shortly after commencing NIV introduces the question of causality. Previous studies on the physiological effect of NIV have shown that CPAP increases intrathoracic pressure and decreases the intracranial venous and spinal outflow, decreasing the flow in the jugular vein by 21%.\(^{13–15}\) Hence, is it conceivable that the pressure changes associated with NIV could have contributed to the development of cerebral ischaemia by reducing the carotid blood flow in an already compromised vessel from previous stenosis as well as thromboevent forming as a result of COVID-19 infection? It is also possible, however, that there is no association between the timing of stroke onset and CPAP, with the stroke purely developing at this time as a consequence of previous risk factors, exacerbated by critical illness or triggered by dislodging a pre-existing thrombus through movement.

The case we have described above clearly demonstrates a mixture of pre-existing cardiovascular disease with a severe COVID-19 pneumonia and severe coagulopathic consequences. However, an interesting additional feature in this case is that the stroke appeared to occur within minutes of commencing CPAP. This case highlights the severity of the potential thrombotic complications that can be associated with SARS-CoV-2 infection. To date, there are no clear guidelines on anticoagulation of COVID-19 patients in the ED, but in view of the emerging evidence this may have to be considered for patients presenting with COVID-19 disease.

**Learning points**

- SARS-CoV-2 infection is associated with prothrombotic events.
- Clinicians must be aware of the potential development of further thrombotic complications during hospital admission.
- Thromboprophylaxis may have a place in the treatment algorithm for COVID-19 patients in the emergency department.

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