Anticoagulation in the obese patient with COVID-19-associated venous thromboembolism

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SUMMARY

A 61-year-old obese man who had recently tested positive for COVID-19 presented to the emergency department following an unwitnessed collapse, with a brief period of unresponsiveness. CT pulmonary angiography confirmed the presence of extensive bilateral pulmonary embolism despite the patient reporting full compliance with long-term dabigatran. The patient was initially anticoagulated with low-molecular-weight heparin and was treated with non-invasive ventilation and dexamethasone for COVID-19 pneumonia. He made a full recovery and was discharged on oral rivaroxaban. His case highlighted some of the common problems encountered when selecting an anticoagulation strategy for obese patients, as well as the lack of definitive evidence to guide treatment decisions. These challenges were further complicated by our incomplete understanding of the underlying mechanisms of COVID-19 coagulopathy, with limited data available regarding the optimal management of thromboembolic complications.

BACKGROUND

The approach to anticoagulation in obese patients is controversial, with limited high-quality evidence available to guide treatment decisions in both acute and chronic settings. The emergence of COVID-19 and its associated thromboembolic complications have further complicated treatment decisions.

We report a case of extensive bilateral pulmonary embolism in a morbidly obese man with active COVID-19 infection despite long-term anticoagulation with dabigatran. This case highlights the lack of evidence regarding the comparative efficacy of anticoagulants in preventing COVID-19-associated venous thromboembolism (VTE). It also underlines some of the challenges surrounding anticoagulation in the obese patient, including choice of therapeutic agent, dosing considerations and logistical issues.

CASE PRESENTATION

A 61-year-old man with a history of morbid obesity, obstructive sleep apnoea and unprovoked pulmonary embolism presented to the emergency department following an unwitnessed collapse at rest. He was independent in self-care at baseline, however his mobility had declined in recent years and he received assistance with instrumental activities of daily living from his wife and daughter. He was a distant ex-smoker who drank minimal alcohol. He used a continuous positive airway pressure device at night for treatment of obstructive sleep apnoea. His only regular medication was dabigatran 110 mg two times per day, with which he reported full compliance.

He had attended the emergency twice in the preceding 9 days with increasing shortness of breath and had been diagnosed with COVID-19 infection on the first occasion. He had likely contracted the virus from his household contacts—both of whom had also tested positive. On the first occasion, he had been clinically stable, and as his routine pathology results and chest X-ray had been reassuring, he had been discharged home with safeguarding advice. He returned to the emergency department 2 days later reporting increasing shortness of breath at rest. Routine bloods including serial troponins and d-dimer were within normal limits and ECG showed sinus rhythm at 79 beats per minute with a normal axis and no acute ischaemic changes. He did not require any supplemental oxygen and was haemodynamically stable. He was discharged home with a prescription for oral prednisolone, azithromycin, esomeprazole and alprazolam.

Over the following 6 days, he reported gradually reduced exercise tolerance and had been staying in bed most of the time. On the day of presentation, he had felt markedly short of breath and had been dizzy on mobilising. His last memory prior to collapsing was of sitting upright in bed. He was subsequently found face down on the floor having sustained significant trauma to his nasal bridge and forehead. His wife reported initially attempting to shake him awake for several minutes with no response. He subsequently regained consciousness and had no obvious postictal features.

At presentation, he was in respiratory distress with a respiratory rate of 32 and peripheral oxygen saturations of 86% of room air. He was haemodynamically stable with a heart rate of 92 and a blood pressure of 135/74 mm Hg. He weighed 145 kg with an estimated body mass index (BMI) of 45.8 kg/m^2. He had numerous superficial grazes over his nasal bridge and left supraorbital region, with localised swelling. Neurological examination revealed no abnormalities and there were no clinical features of a facial bone fracture. Heart sounds were audible with no murmurs. There were coarse crackles on auscultation of the left lung mid zone.

INVESTIGATIONS

Point of care arterial blood gas showed type 1 respiratory failure with an estimated alveolar–arterial gradient of 59.8 kPa. Serial laboratory investigations (table 1) showed a marked elevation in both high sensitivity troponin and d-dimer. ECG showed sinus rhythm, with a new right bundle

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Table 1 Initial laboratory investigations

Test	First presentation (day 0)	Second presentation (day 2)	Third presentation (day 9)	Reference range
Urea	3.8	4.1	6.5	1.7–8.3 mmol/L
Sodium	136	138	141	133–145 mmol/L
Potassium	4.1	4.1	4.2	3.5–5.1 mmol/L
Chloride	99	103	106	95–110 mmol/L
Creatinine	83	76	88	62–106 mmol/L
Alanine Aminotransferase (ALT)	135	148	70	8–41 U/L
Gamma-glutamyl transferase (GGT)	49	61	78	8–61 U/L
Alkaline phosphatase	51	48	35	40–130 U/L
Total bilirubin	6.6	5.4	14.1	2.5–21 µmol/L
C-reactive protein (CRP)	8	14	56	0.2–5 mg/L
Lactate Dehydrogenase (LDH)	263	263	353	135–225 U/L
Troponin (high sensitivity)	9	9	229	0–14 ng/L
Haemoglobin	158	160	160	13.5–17.5 g/L
Platelets	168	131	108	140–400×10^9
White Blood Cell Count (WBC)	4.00	3.27	7.86	4–11×10^9
Neut Abs	2.19	1.59	6.33	2–7×10^9
Lymph Abs	0.98	1.13	0.86	1–4×10^9
Prothrombin time	16.4	15.8	17.9	11.5–15 s
International Normalized Ratio (INR)	1.2	1.1	1.3	n/a
Activated Partial Thromboplastin Time (APTT)	32.2	30.2	30.9	27–37 s
D-dimer	206.2	284.1	>10 000	0–500 ng/mL

branch block pattern. Chest X-ray was of limited value due to the patient's body habitus and logistical difficulties related to image acquisition. In the absence of chest pain, it was felt that the clinical presentation was most in keeping with acute pulmonary embolism in the setting of active COVID-19 pneumonia. The hypoxemia was thought to be multifactorial, relating to the combination of acute pulmonary embolism, COVID-19 pneumonia and obesity hypoventilation syndrome.

Initial management was complicated by the presence of head trauma in a patient on anticoagulation. A CT scan of the brain and cervical spine was performed to exclude intracranial haemorrhage or spinal fracture. Low-molecular-weight heparin (LMWH) was administered at a dose of 100 mg two times per day. High flow humidified oxygen was administered, before switching to continuous positive airway pressure (CPAP) therapy once an appropriate mask could be located given the extensive grazing over his nasal bridge. He was transferred to the intensive care unit and commenced on oral dexamethasone 8 mg once daily.

Serial high sensitivity troponin assays were downtrending, and repeat arterial blood gas sampling showed adequate oxygenation on CPAP. CT pulmonary angiography revealed bilateral near confluent pulmonary embolism, extending from the distal right and left pulmonary arteries through both lower lobe segmental branches. There was no CT scan evidence of right ventricular strain.

TREATMENT

The patient responded well to CPAP and was monitored in the ICU for 48 hours before being discharged to an isolation ward. He was treated with enoxaparin 100 mg two times per day and a 10-day course of oral dexamethasone 8 mg once daily. Over the following days, he was gradually weaned off oxygen and was regularly reviewed by a multidisciplinary team including a physiotherapist, occupational therapist and a dietician. He made good progress and was deemed safe for discharge home on the 9th day after admission. He was discharged on oral rivaroxaban 20 mg daily.

OUTCOME AND FOLLOW-UP

Follow-up visits were arranged with community occupational therapy and respiratory nurse services. Three months post discharge, the patient had made a good recovery and felt he was close to his premorbid baseline. He was awaiting an appointment with his local haematology service for review of his anticoagulation. He was also referred to the local obesity clinic for ongoing care.

DISCUSSION

The precise mechanisms underlying COVID-19-associated coagulopathy remain under investigation.[1–3] While it is clear that patients with COVID-19 are at significantly increased risk of thromboembolic complications, there is a lack of robust evidence to guide treatment decisions regarding anticoagulation. This case demonstrates that patients with acute COVID-19 infection may be at risk of developing potentially life-threatening venous thromboembolic disease even while reporting full compliance with a non-vitamin K antagonist oral anticoagulant (NOAC). Treatment decisions in this case were further complicated by uncertainty surrounding the efficacy of NOACs in obese patients.

Interim guidance documents have been produced by multiple bodies including the International Society on Thrombosis and Haemostasis (ISTH),[4] the American Society of Haematology and the American College of Chest Physicians (ACCP).[5] These documents recommend the use of LMWH as the first-line anticoagulant for both prophylaxis and treatment of VTE in patients hospitalised with COVID-19 in the absence of contraindications. These recommendations are based on evidence that LMWH

may reduce mortality, through both anticoagulant and anti-inflammatory effects.[6]

The optimal choice of therapeutic agent on discharge is less certain. The ACCP recommends the use of weight-adjusted LMWH for patients who develop recurrent VTE despite compliance with oral anticoagulation.[6] However, we had significant concerns about this patient's ability to reliably self-administer LMWH at home. The patient himself expressed a preference for oral therapy. There were multiple barriers to ensuring effective warfarin monitoring on discharge including logistical concerns regarding patient transport, difficult venous access and availability of warfarin monitoring clinics during the COVID-19 pandemic. Combining these considerations with the fact that he had been stable for years on dabigatran and that the acute inflammatory phase of his illness had passed, we felt that ongoing lifelong therapy with a NOAC would be the best option for this patient.

This decision was further complicated by the uncertainty surrounding efficacy of NOACs in patients with morbid obesity. The ISTH published guidelines in 2016 which recommended against the use of NOACs in patients who weigh >120 kg or have a BMI >40 kg/m^2.[7] This was primarily due to a lack of sufficient clinical data and concerns about the possibility of underdosing obese patients. When NOACs are used in this population, the guidelines recommend measurement of drug-specific peak and trough levels. Unfortunately, therapeutic monitoring is not routinely available in many institutions at this time.

However, since these guidelines were published, at least two retrospective studies have compared clinical outcomes between NOACs and warfarin in obese patients.[8 9] Neither study demonstrated a significant difference between agents in terms of bleeding or recurrence of VTE. Of note, rivaroxaban was the most commonly used NOAC in both studies. Conversely, dabigatran was only used in 3% of patients in one study and was not used at all in the other.

Furthermore, it has been suggested that the pharmacodynamic and pharmacokinetic parameters of rivaroxaban are only minimally affected by obesity, even among patients weighing >120 kg, owing to its limited volume of distribution.[10] The data for apixaban are less convincing, with an increased volume of distribution and reduced half-life observed in obese patients.[11] A recent systematic review suggested that obesity may have a clinically significant impact on the efficacy of dabigatran.[12] There is limited evidence available regarding edoxaban in this patient cohort. Based on this evidence, we felt that rivaroxaban would be the best choice for this patient.

It is unclear whether our patient's recurrent VTE was related to the attenuated effect of dabigatran in an obese patient, inefficacy of a NOAC in the setting of active COVID-19 or unreliable reports of compliance with medication. Regardless, this man's case highlights the need for more evidence to inform the optimal choice of anticoagulant both in the setting of COVID-19 and in morbid obesity.

Learning points

- Pulmonary embolism should be considered in the differential of all patients with COVID-19 infection presenting with hypoxia, even if they report full compliance with existing non-vitamin K antagonist oral anticoagulant treatment.
- Further research is required to elucidate the precise mechanisms underlying COVID-19-associated coagulopathy. Low-molecular-weight heparin appears to be an appropriate agent for use in hospitalised patients based on current evidence.
- There is limited evidence to guide the choice of agent when anticoagulating obese patients with venous thromboembolism . Treatment decisions should be made on a case by case basis, with due consideration given to individual patient factors such as treatment indication, bleeding risk, compliance, logistical considerations and patient preference.

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