Antithrombin III deficiency-induced coagulopathy in the context of COVID-19: a case series

A coagulopathy associated with coronavirus disease 2019 (COVID-19) has been repeatedly described within the literature.[1] Diffuse endothelial inflammation has been reported affecting both the renal and pulmonary vasculature on autopsy.[2,3] A consequence of this appears to be widespread thrombi formation and the organs affected are hypothesised to determine the phenotype of the disease. Significant elevations of D-dimer and fibrinogen have been reported and are strong predictors of mortality.[4] Hence, the use of routine anticoagulation has been proposed as a therapeutic modality.

Our large south London Hospital Trust, King's College Hospitals, UK, had admitted and treated 239 patients with COVID-19 in our critical care facilities at the time of data collection for the present case series. Observing the increased incidence of thromboembolic events amongst patients with COVID-19, a multidisciplinary decision was taken to double our standard dose of thromboprophylaxis and have a low threshold for pre-emptive therapeutic anticoagulation.

Heparins are often the anticoagulant of choice, being titratable, versatile and reversible. However, we observed difficulties achieving therapeutic anticoagulation for some patients. This was especially evident for patients receiving renal replacement therapy (RRT) who had increased coagulation-related complications; their circuits clotted regularly.

We hypothesised that an acquired deficiency of antithrombin III (ATIII), related to the COVID-19 pathology, was the causative mechanism. In response, we began a practice of anticoagulating RRT circuits with epoprostenol and using argatroban (a direct thrombin inhibitor) for systemic anticoagulation.

To guide clinical practice, we began routinely testing ATIII levels in patients with COVID-19 admitted to a single critical care unit within our hospital's organisation. All patients had severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) confirmed by reverse transcriptase polymerase chain reaction and/or compelling radiographic evidence. Of the 19 patients tested during this period, five (26%) had a demonstrable ATIII deficiency.

In particular, we describe two patients who subsequently developed bilateral pulmonary emboli despite one receiving therapeutic intravenous heparin, and the other, prophylactic low-molecular-weight heparin. Table I details their critical care admission findings and anticoagulation status at the point of their thromboembolism diagnosis. Both presented with typical features of COVID-19 disease inclusive of cough, fever and breathlessness. After brief periods with external oxygen therapy they progressed to hypoxaemic respiratory failure.

ATIII deficiency is uncommon, either being acquired or a rare autosomal hereditary disorder.[5] It results in a prothrombotic state, due to lack of its usual function in inactivating thrombin, factor Xa and other proteases. Heparins function as an anticoagulant by potentiating ATIII activity, up to 1000-fold. This explains its lack of efficacy, and why thromboembolic events occurred despite heparinisation.

Given these results, physicians should consider the regular testing of ATIII titres for patients with COVID-19. If deficient, both a mechanistically alternative form of anticoagulation, or ATIII replacement therapy, may be warranted. Careful thought should be given to pre-emptive therapeutic anticoagulation.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Andrew J. Gardner and Daniel J. Kirkin: design of the work, acquisition and interpretation of data, drafting the work and revising it critically. Sancho Rodriguez-Villar and Gonzalo Leoz Abellanas: conception of the work and revising it critically. Alice Tee: our redeployed radiologist trainee who helped during the study scanning the patients for DVT (deep vein thrombosis) and reporting CT-scans. Antonio Valentin: final external critical revision.

Ethics approval

Not applicable. ATIII levels were performed with the potential to guide clinical practice and the data was collected retrospectively.

Consent for publication

Patient 1 dataset

Consent for publication of raw data was not obtained but the dataset is anonymous in a manner that can easily be verified by any user of the dataset. Publication of the dataset clearly and obviously presents minimal risk to confidentiality of study participants. We were unable to gain consent due to

Table I. Demographics, clinical history, investigations and relevant coagulation studies of two patients with COVID-19.

	Patient 1	Patient 2
Demographics		
Age, years	61	73
Sex	Male	Male
Baseline dependency	Independent	Independent
Body mass index, kg/m^2	25·5	27·7
Admission findings		
Past medical history	Ischaemic heart disease, type 2 diabetes mellitus, hypertension, atrial flutter	Nil
Symptoms at disease onset	Cough, breathlessness, fevers, myalgia, headache	Breathlessness, altered taste and smell, fevers
Days from onset of first symptoms to hospital admission	6	10
Radiographic features on admission – chest X-ray	Bilateral peripheral airspace opacification, right upper zone consolidation.	Bilateral patchy infiltrates with associated basal pleural effusion, left basal consolidation.
Treatment prior to ICU admission	CPAP trial, intravenous antibiotics	CPAP trial, intravenous antibiotics
COVID-19 diagnosis	Positive RT-PCR for SARS-CoV-2	Negative RT-PCR for SARS-CoV-2 but strong clinical suspicion and radiographic evidence
Admission to ICU		
Days from onset of first symptoms to ICU admission	11	15
Disease severity (APACHE II)	Critical (8)	Critical (11)
P/F ratio	145	142
Laboratory findings on ICU admission		
WCC (3·7–9·5), × 10^9/l	18·7	11·7
Neutrophil (1·7–6·1), × 10^9/l	16·1	9·8
Lymphocytes (1–3·2), × 10^9/l	0·7	0·5
Monocytes (0–0·8), × 10^9/l	1·9	1·2
Platelets (140–400), × 10^9/l	410	159
Haemoglobin (133–167), g/l	132	113
Albumin (25–35), g/l	28	25
Alanine aminotransferase (5–55), iu/l	40	61
Aspartate aminotransferase (5–38), u/l	28	42
Lactate dehydrogenase (0–240), u/l	540	470
Creatinine (45–120), μmol/l	80	64
Creatine kinase (25–175), u/l	50	30
eGFR, ml/min/1·73 m^2	85	>90
Troponin T (0–14), ng/l	60	29
C-reactive protein (0–5), mg/l	186	153
Serum ferritin (30–400), μg/l	1678	2123
Procalcitonin (0·02–0·05), μg/l	0·2	0·28
NT-proBNP, pg/ml	2375	1178
Fibrinogen (2·0–5·0), g/l	4·3	7·4
D-dimer	12 838	32 155
Coagulation testing		
Antithrombin III level (NR: 80–130%)	60	76
Objective thromboembolism	CTPA demonstrating bilateral lobar, segmental and subsegmental pulmonary embolism	CTPA demonstrating bilateral multiple, linear thrombus in the segmental and subsegmental branches of the upper and lower lobar branches of the pulmonary artery
Anticoagulation at the point of thromboembolism	Systemic intravenous heparin	Subcutaneous low-molecular-weight heparin

Table I. (*Continued*)

	Patient 1	Patient 2
Coagulation intent (dose)	Therapeutic (2000 u/h)	Prophylactic (40 mg once daily)
INR	1·2	1·1
Activated partial thromboplastin time ratio	1·3* (intended target: 2·0–2·5)	0·9 (intended target: N/A)
Outcome		
Did they require renal replacement therapy?	Yes	No
Days of ICU admission	16	–
Deceased, recovered or ongoing illness	Deceased	Recovered to discharge

APACHE II, Acute Physiology And Chronic Health Evaluation II; COVID-19, coronavirus disease 2019; CPAP, continuous positive airway pressure; CTPA, computed tomography pulmonary angiography; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; INR, international normalised ratio; NT-proBNP, N-terminal pro-brain natriuretic peptide; P/F ratio, the ratio of arterial oxygen partial pressure to fractional inspired oxygen; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; WCC, white cell count.

*Very labile coagulation, with significant difficulty achieving a heparin dose which would achieve the target range.

the patient's death prior to collection of the data, only three indirect identifiers are included in the dataset (age, sex and body mass index) therefore constituting minimal risk of a confidentiality breach. The daughters of the patient in question were informed and were happy for the data to be published, representing the likely view of the patient. The benefit is to further inform the medical community on emerging issues in COVID-19 disease. The dataset was reviewed by our Caldicott guardian (Dr Alistair Baker) and our data protection officer (Nick Murphy-Okane) at King's College Hospitals NHS trust, both agreed the risk of confidentiality breach was minimal and there is benefit to the medical community in publishing the data.

Patient 2 dataset

Written consent for publication of raw data obtained from study participant.

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Data availability

The datasets used and/or analysed during the present study are available from the corresponding author on reasonable request.

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