Terminal complement inhibition dampens the inflammation during COVID-19

Emerging evidence suggests that activation of the complement system is critical in the pathogenesis of the novel coronavirus, SARS-CoV-2, the causative agent of COVID-19-related lung injury. Inhibition of the terminal complement pathway by targeting complement protein 5 (C5) may be an effective therapeutic intervention in CoV-mediated disease.[1] Paroxysmal nocturnal haemoglobinuria (PNH) is a rare, acquired haematopoietic stem cell (HSC) disease characterised by intravascular haemolysis, increased thromboembolic risk and bone marrow failure.[2] The lack of GPI-linked complement regulators, especially CD55 and CD59, makes PNH erythrocytes exquisitely sensitive to complement activation, which can occur continuously, spontaneously and acutely and lead to devastating complications as a result of uncontrolled intravascular haemolysis. Precipitation of haemolysis, both in untreated patients and in those on anti-complement therapy,[3] can be induced by any complement-activating events such as infection, trauma, surgery and pregnancy. Although viral infections have been shown to induce haemolysis by activating complement, there has been no published report of COVID-19 in the context of PNH during the ongoing pandemic, and neither has the added benefit of therapeutic complement inhibition, especially with monoclonal antibodies targeting C5 including eculizumab and ravulizumab, been examined.

Here we report the clinical course, degree of intravascular haemolysis and outcomes of COVID-19 in four patients with PNH, two well-established on terminal complement inhibitor and two treatment-naïve PNH patients.

Our index patient (patient 1, Table I) presented in mid-March 2020 with symptoms of fever (39·1°C), myalgia, dry cough and anosmia. She had a long-standing history of PNH and her disease activity, symptoms and haemolysis were well controlled on a long-acting C5 inhibitor, ravulizumab,[4] and prior to this with a first generation monoclonal antibody, eculizumab.[3] She was not hypoxic. SARS-CoV2 infection was confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) assay. She did not have elevated inflammatory markers and her chest radiology was normal. Interestingly, her haemolytic markers were not significantly elevated, and terminal complement was adequately inhibited, as measured by an undetectable CH50/AH50.

Subsequently, we identified three additional PNH patients with concurrent presentation with clinical symptoms of COVID-19 and RT-PCR-confirmed COVID-19 (Table I). Two patients naïve to complement inhibitor treatment (patients 3 and 4), both with moderate/large PNH clones accompanied by a degree of haemolysis, required hospitalisation for COVID-19 pneumonia and also showed active signs of inflammation [high C-reactive protein (CRP)] and worsening haemolysis [high lactate dehydrogenase (LDH) compared to baseline], due to uncontrolled complement activation. The clinical course of these two individuals, not on anti-complement therapy but on primary prophylaxis with warfarin, was protracted and needed prolonged hospitalisation, readmission and supplemental oxygen therapy. Patient 2, on a high dose of eculizumab, had a similar presentation to the index patient and was found to be anaemic requiring blood transfusion, but with a clear chest radiograph, normal CRP and normal LDH.

It is clear that complement plays a key role and is an integral component of the innate immune response to pathogens and its dysregulation or activation, either due to acquired deficiency of complement regulatory proteins (i.e. PNH) or due to viral infection (i.e. SARS-CoV-2), and can lead to significant tissue damage and importantly thrombosis due to endothelial damage.[5] Our patients illustrate the presence of both conditions (PNH and COVID-19) concurrently and the differential response seen in patients already on effective complement inhibition compared to patients not on C5 inhibition. The beneficial effect of complement inhibition in not only controlling the intravascular haemolysis due to PNH, but also dampening the hyperinflammatory lung damage during COVID-19 has been illustrated with our small series. The adverse effect in patients not on C5 inhibitors may be circumstantial, as other known COVID-19 risk factors of mortality and morbidity,[6] like older age, comorbidity, high body mass index (BMI) and male gender could have contributed to the worse outcome.

SARS-CoV-2 infection,[7] like other virus infections such as influenza virus and respiratory syncytial virus, is likely to induce massive complement activation in this 'vulnerable' group and can lead to severe life-threatening complications and hospitalisation. Emerging evidence suggests that the activation of the complement system, even in the absence of PNH, is key in the pathogenesis of COVID-19-related lung injury[8] and therefore C5 inhibition may be an effective therapeutic strategy in CoV-mediated disease. Trials (SOLID-C19, CORIMUNO19-ECU and ALXN1210-COV-305), are ongoing to test the efficacy of terminal complement inhibition in dampening the progression of complications and improve outcomes in patients with COVID-19·[9]

Table I. Clinical, demographic and baseline risk factors and progress of paroxysmal nocturnal haemoglobinuria (PNH) patients with concurrent COVID-19.

	Patient 1	Patient 2	Patient 3	Patient 4
Age/ sex	35/F	37/F	51/M	47/M
Demographics	Caucasian	Caucasian	Southeast Asian	Caucasian
BMI (NR 18·5–24·9)	25·1	26·1	32·8	32·7
Previous AA	No	Yes	Yes	No
Comorbidity	None	None	Type 2 DM, HTN, CKD	Type 2 DM
Prophylactic anti-coagulation	No	No	Yes/warfarin	Yes/warfarin
PNH clone (G/M/E)[@]	90/90/60	99/98/64	49/49/20	31/36/25
Anti-complement therapy (type/duration of therapy)	Yes Ravulizumab 3300 mg × 8 weekly 6 years	Yes Eculizumab 1500 mg × 2 weekly 11 years	No	No
Baseline LDH (NR < 240) IU/l	168 (1670*)	210 (2574*)	500 (NA*)	157 (NA*)
Symptoms	Fever, sore throat, myalgia	Fever, headache, cough, myalgia	Fever, cough, abdominal pain, fatigue, myalgia	Fever, abdominal pain, nausea, cough
COVID status	Positive	Positive	Positive	Positive
Hospitalised, duration of stay	No	No	Yes, 4 days	Yes, 2 days and readmitted for 5 additional days
CRP (NR < 5 mg/l)	5	10·4	26	29
LDH IU/L (NR < 240)	307	258	785	358
Ferritin (NR 13–150 μg/l)	ND (212)	8047 (5858[†])	1487 (283)	ND (153)
Lymphocytes (1·3–4 × 10^9/l)	0·6 (1·3)	0·6 (0·91)	0·6 (1·47)	1·2 (2·1)
Oxygen saturations	98%	99%	89%	91%
Oxygen requirement	Room air	Room air	2 litres	2 litres
Chest X ray	Normal	Normal	Confluent air space shadowing	Peripheral ground glass opacity
Thrombotic complications	No	No	No	No
Sequelae	Resolved	Resolved	Resolved	Readmitted with worsening symptoms

F, female; M, male; BMI, body mass index; NR, normal range; AA, aplastic anaemia; DM, diabetes mellitus; HTN, hypertension; CKD, chronic kidney disease; PNH, paroxysmal nocturnal haemoglobinuria; G, granulocyte clone; M, monocyte clone; E, erythrocyte/red cell clone (both type II and type III); LDH, lactate dehydrogenase; ND, not done.

*Results in parentheses indicate LDH level pre anticomplement therapy for patients 3 and 4. NA, not applicable for patients 1 and 2.

[†]Patient had transfusion-related iron overload with high baseline ferritin and was on iron chelation with oral deferasirox film-coated tablets 1080 mg/day.

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Pulmonary artery thrombectomy – a life-saving treatment in a patient with presumed COVID-19 complicated by a massive pulmonary embolus

As new evidence emerges regarding the abnormal coagulation status in patients with novel coronavirus pneumonia (NCP), we are seeing more patients with venous thromboembolic (VTE) disease.[1,2] Hypercoagulability is not solely responsible for this evolving phenomenon; the other two variables in Virchow's triad, namely venous stasis and epithelial injury are also fulfilled as patients lie immobile for prolonged periods on the intensive care unit (ICU).[3]

New guidelines regarding thrombosis prevention and coagulopathy treatment have been published by Thrombosis UK to keep up with the ever changing management of patients with this unpredictable disease.[4]

Case report

We discuss a patient with massive pulmonary embolism (PE) and suspected coronavirus disease 2019 (COVID-19) with classic chest X-ray (CXR), computed tomography (CT)[5] and clinical findings. A 58-year-old male presented to the emergency department by ambulance with a 9 day history of shortness of breath, non-productive cough and feeling generally unwell. He had been self-isolating for the last 10 days, denied foreign travel and had no known COVID-19 contacts. He lived with his wife who also reported less severe symptoms of cough and shortness of breath. He was previously fit and well and on no regular medication.

On examination he had increased work of breathing and was unable to speak in full sentences. His heart sounds were normal and his abdomen was soft. His calves were soft and non-oedematous. His Glascow Coma Score was 15/15. His blood results were as follows: international normalised ratio (INR) 1·1, activated partial thromboplastin time (aPTT) 22·7 s and fibrinogen was raised at >6 g/l. His white cell count was raised at $21{\cdot}3 \times 10^9$/l with a lymphopaenia of $0{\cdot}98 \times 10^9$/l and neutrophil count of $18{\cdot}5 \times 10^9$/l. Haemoglobin, hepatic function and renal function was normal. A nasopharyngeal swab to isolate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was negative. The