COVID-19 infection in patients on anti-complement therapy: The Leeds National Paroxysmal Nocturnal Haemoglobinuria service experience

Following a recent case series in the BJH,[1] we report our experience of COVID-19 from the Leeds Paroxysmal Nocturnal Haemoglobinuria (PNH) national service. Understanding the pathophysiology of the novel coronavirus, SARS-CoV-2, responsible for the COVID-19 pandemic is needed to develop effective treatments. Inflammation as a consequence of the host immune response is increasingly recognised in development of serious complications.[2,3] Critically ill patients develop an ARDS-like illness, with over-activation of complement and coagulation pathways implicated in tissue damage.[4-7] Consequently, immunomodulatory therapies represent a logical investigational approach. Several complement inhibitors are under investigation (NCT04346797, NCT04355494, NCT04288713, NCT04369469, NCT04390464) and Diurno et al.[8] reported positive outcomes from 4 ITU patients treated with eculizumab. Complement inhibitors already have established roles in treatment of several rare diseases including PNH. Kulasekararaj et al.[1] recently suggested that patients on C5 inhibitors may have a milder disease course based on 4 patients with PNH and COVID-19, 2 of whom were on eculizumab. Our first 4 cases (characteristics in Table 1) were less fortunate, requiring hospitalisation despite complement inhibition; one of these patients died of COVID-19.

PNH is a rare clonal haematological disorder due to an acquired PIG-A gene mutation in haematopoietic stem cells, leading to a lack of glycosylphosphatidylinositol (GPI)-anchored proteins on haematopoietic cells. This leads to risk of thromboembolic disease and complement-mediated haemolysis.[9] Complement inhibitors have revolutionised PNH management and established treatments target terminal complement protein 5 (C5) with the monoclonal antibody eculizumab (Soliris™) and latterly the longer acting ravulizumab (Ultomiris™). Several other complement inhibitors are in trial or development. C5 is important in innate immune defence against Neisserial infection, thus there is risk of meningococcal sepsis with C5 inhibition. Our centre has 18 years' experience using complement inhibitors and currently has 618 patients, with 237 on anti-complement therapy.

Patient 1

A 61-year-old female patient with PNH since 2008, established on ravulizumab and requiring intermittent blood transfusions, was admitted in March 2020 with fever, lethargy, dry cough and diarrhoea. Anosmia and ageusia were also reported. She had received her scheduled ravulizumab that day. Co-morbidities comprised tuberous sclerosis, renal angiomyolipomas and epilepsy. Upon admission she had breakthrough haemolysis with LDH 2·7 times the upper limit of normal (ULN) and she required a blood transfusion. Chest X-ray (CXR) demonstrated bilateral pneumonia highly suspicious for COVID-19 (Fig 1). Reverse transcriptase polymerase chain reaction (RT-PCR) testing from two nasopharyngeal swabs were negative but she was treated for COVID-19 based on characteristic radiographic appearances and high clinical suspicion. She had significant hypoxia requiring 40% oxygen and antibiotics for secondary bacterial pneumonia but responded to treatment and was discharged after 8 days.

Patient 2

A 47-year-old male patient with PNH diagnosed in 2016, established on eculizumab since 2017, was admitted to hospital in March 2020. He had a background of aplastic anaemia since 2011, recently transformed to myelodysplastic syndrome and was awaiting bone marrow transplantation. He was admitted with fever, myalgia and dizziness. Comorbidities included psoriasis, psoriatic arthropathy (off treatment) and hypercholesterolaemia. COVID-19 RT-PCR testing was positive. He was treated with intravenous antibiotics to cover bacterial infection, his symptoms quickly resolved and he was discharged after 5 days. Of note, COVID-19 RT-PCR testing remained positive for 8 weeks, long after symptom resolution. The first negative result was 9·5 weeks post admission and has since remained negative.

Patient 3

A 43-year-old male patient was admitted to hospital in March 2020 with a 10-day history of symptoms of suspected COVID-19. He had a history of aplastic anaemia in 2005, developed haemolytic PNH in 2008 and was on eculizumab since 2015. He also had type 2 diabetes mellitus requiring metformin. He had breakthrough haemolysis with haemoglobinuria, Hb 60 g/dl and LDH significantly raised (4·9 × ULN). COVID-19 RT-PCR was positive. He received an extra dose of eculizumab on admission and 4 units

British Journal of Haematology, 2020, **191,** e1–e4
First published online 18 September 2020
doi: 10.1111/bjh.17097

Table I. Demographics of patients with PNH previously established on anti-complement therapy on admission to UK hospitals with clinical COVID-19 infection.

	Patient 1	Patient 2	Patient 3	Patient 4
Age (y)	61	47	43	77
Sex	F	M	M	F
Ethnicity	White	BME	BME	White
Co-morbidity	Tuberous sclerosis, bilateral renal angiomyolipomas, hypothyroidism	AA recently transformed to MDS, psoriasis and psoriatic arthropathy, hypercholesterolaemia	AA, Type 2 diabetes mellitus	AA, Parkinson's disease, iron overload
PNH clone size (%):				
Neutrophils	99·09	98·10	99·51	99·53
Monocytes	98·63	98·86	97·93	99·53
Erythrocytes	35·44	46·96	89·47	15·17
(Type II/ Type III)	(0·3/35·13)	(22·13/24·83)	(3·35/86·12)	(1·71/13·46)
Reticulocytes	95·08	94·28	99·64	92·07
Anticoagulation	No	No	Yes (warfarin)	No
Anti-complement therapy regime;	Ravulizumab 3300 mg every 8 weeks	Eculizumab 1200 mg every 2 weeks	Eculizumab 900 mg every 2 weeks	Eculizumab 900 mg every 2 weeks
Number of days (d) prior to admission last dose given	On day of admission	6	5	8
Duration of anti-complement therapy prior to admission	11 y 8 m (2 y 2 m ravulizumab; prior to this 9 y 6 m eculizumab)	2 y 7 m (1 y 7 m 1200 mg dose)	4 y 4 m	6 y 7 m
Symptoms COVID-19	Dry cough, diarrhoea, abdominal pain, fever, anosmia, ageusia	Fever, myalgia, dizziness	Dyspneoa, fever, dark urine	Dyspnoea, chest pain
CRP mg/l, max during admission (reference range <10)	332	28	382	61·9
LDH IU/l, max during admission (reference range)	819 (120–246)	Not done	1377 (80–240)	501 (120–246)
Lymphocytes on admission (reference range) ×10·9/l	0·43 (1–4·5)	0·19 (1–4·5) drop from usual baseline of 0·6-0·9	1·3 (1·1–5)	0·31 (1–4)
Duration of admission (d)	8	5	23	12
COVID-19 nasopharyngeal swab RT-PCR	Negative	Positive	Positive	Positive
CXR	Peripheral bilateral consolidation highly suspicious of COVID-19	Normal	Bilateral widespread consolidation	Right lower lobe infiltrate
Maximum oxygen requirement	Venturi mask, 40%, 10 l/min	Room air	Maximal oxygen support	Room air
Ventilator support	No	No	Yes (Intubated)	No
Evidence of breakthrough haemolysis during admission	Yes	No	Yes	Yes
Additional doses of complement inhibitor	No	No	Yes (d 1, 10 and 19 of admission)	No
Outcome	Recovered	Recovered	Died	Recovered

F, female; M, male; CRP, C-reactive protein; LDH, lactate dehydrogenase; CXR, chest X-ray; AA, Aplastic anaemia; d, days; y, years; m, months; BME, black and minority ethnic.

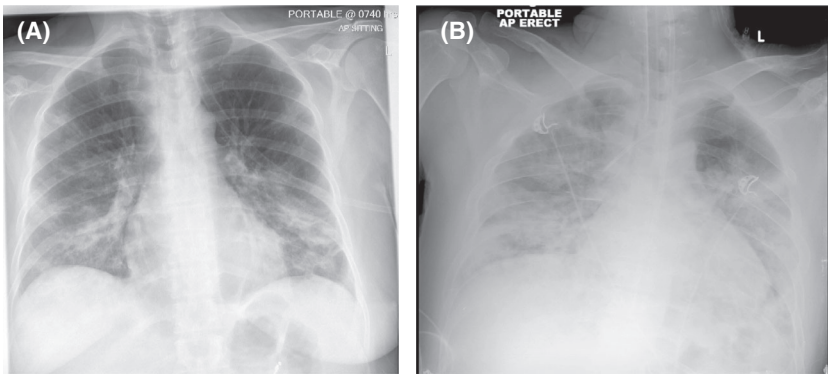

Fig 1. (A) Portable AP chest X-ray (CXR) showing peripheral bilateral consolidation highly suspicious for COVID-19 infection in Patient 1 (day 4 of admission). (B) CXR showing widespread bilateral consolidation in Patient 3 (day 18 of admission).

packed red cells. After 4 days he required intensive care admission for mechanical ventilation due to worsening respiratory failure. He received broad-spectrum antibiotics for bacterial infection and further doses of eculizumab for ongoing haemolysis. Unfortunately, he deteriorated despite maximal multi-organ support and died 23 days after admission.

Patient 4

A 77-year-old female patient was admitted to hospital from a nursing home in April 2020 with breathlessness and chest pain. She had a history of aplastic anaemia diagnosed in 2007, now on third line therapy, and symptomatic PNH treated with eculizumab since 2013. Co-morbidities comprised Parkinson's disease and iron overload. Upon admission her Hb was 54 g/l, COVID-19 RT-PCR positive and CXR demonstrated right lower lobe consolidation. She received antibiotics for secondary bacterial pneumonia, 4 units of packed red cells and her scheduled eculizumab on day 3 of admission. She recovered and was discharged after 12 days.

Discussion

Here we report four cases of COVID-19 infection requiring hospitalisation including one fatality, whilst already receiving a complement inhibitor. All patients had risk factors for more serious illness as seen in patients 1 and 3, although patient 2 had a relatively mild course. These patients represent our most severe cases as they required hospitalisation. The true prevalence of COVID-19 in our population remains unknown without serological testing. Since March 2020 7 further patients on complement inhibitors have reported possible COVID-19 symptoms. Two of 7 were hospitalised and treated for chest infections but RT-PCR was negative and CXR not typical for COVID-19. Five of 7 had milder symptoms and self-isolated at home as per guidelines.

There is evidence of increased activation of coagulation pathways and susceptibility to thromboembolic disease in patients with COVID-19,[10] though we did not detect any thrombotic complications in these cases. This could be due to complement inhibitor treatment. Infections increase risk of breakthrough haemolysis in PNH due to increased activation of the complement system, overwhelming complement blockade. COVID-19 induced breakthrough haemolysis was seen in 3 of our four patients, thus representing an additional concern in our population.

The use of complement inhibitors to attenuate immune mediated damage in COVID-19 nevertheless represents a very interesting theoretical approach. However, careful consideration as to which patients may benefit will be required and the outcome of clinical trials needed.

Author contributions

AP - wrote, edited and reviewed the manuscript. PM - reviewed and edited the manuscript. TM - reviewed and edited the manuscript. LM - reviewed and edited the manuscript. LA - reviewed and edited the manuscript. KR - reviewed the manuscript. NH - reviewed the manuscript. BF - reviewed the manuscript. JG - reviewed the manuscript. PH - reviewed and edited the manuscript. MG - reviewed and edited the manuscript.

Alexandra Pike[1,2]
Petra Muus[1]
Tahla Munir[1]
Lindsay Mitchell[3]
Louise Arnold[1]
Kathryn Riley[1]
Nicola Houghton[1]
Briony Forrest[1]
Jeanifer Gachev[1]
Peter Hillmen[1,2]
Morag Griffin[1]

[1]Department of Haematology, Leeds Teaching Hospitals NHS Trust, Leeds, [2]Section of Experimental Haematology, Leeds Institute of Medical Research at St. James's, School of Medicine, University of Leeds and [3]Department of Haematology, University Hospital Monklands, Airdrie, Lanarkshire, UK.
E-mail: alexandra.pike@nhs.net

References

1. Kulasekararaj A, Lazana I, Large J, Posadas K, Eagleton H, Lord Villajin J, et al. Terminal complement inhibition dampens the inflammation during COVID-19. *Br J Haematol*. 2020;**190**(3):e141–3.
2. Risitano AM, Mastellos DC, Huber-Lang M, Yancopoulou D, Garlanda C, Ciceri F, et al. Complement as a target in COVID-19? *Nat Rev Immunol*. 2020;**20**(6):343–4.
3. Fletcher-Sandersjöö A, Bellander BM. Is COVID-19 associated thrombosis caused by overactivation of the complement cascade? A literature review. *Thromb Res*. 2020;**194**:36–41.
4. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. *Transl Res*. 2020;**220**:1–13.
5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;**395**(10229):1054–62.
6. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia *J Thromb Haemost*. 2020;**18**(4):844–7.
7. Gralinski LE, Sheahan TP, Morrison TE, Menachery VD, Jensen K, Leist SR, et al. Complement activation contributes to severe acute respiratory syndrome coronavirus pathogenesis. *mBio*. 2018;**9**(5):e01753-18.
8. Diurno F, Numis F, Porta G, Cirillo F, Maddaluno S, Ragozzino A, et al. Eculizumab treatment in patients with COVID-19: preliminary results from real life ASL Napoli 2 Nord experience. *Eur Rev Med Pharmacol Sci*. 2020;**24**(7):4040–7.
9. Hillmen P, Lewis S, Bessler M, Luzzatto L, Dacie J. Natural history of paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 1995;**333**(19):1253–8.
10. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb. Res*. 2020;**191**:9–14.