

Haemolytic anaemia: a consequence of COVID-19

Memoona Jawed,^{1,2} Elizabeth Hart,³ Malik Saeed⁴

¹Queen's Medical Centre, Nottingham University Hospital NHS Trust, Nottingham, UK

²Acute Medicine, Queen's Medical Centre, Nottingham University Hospital NHS Trust, Nottingham, UK

³Acute Medicine, Nottingham University Hospitals NHS Trust, Nottingham, UK

⁴Haematology, Nottingham University Hospitals NHS Trust, Nottingham, UK

Correspondence to

Dr Memoona Jawed;
memoona.jawed@nuh.nhs.uk

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SUMMARY

A man in his early 50s presented with jaundice, mild shortness of breath on exertion and dark urine. He had had coryzal symptoms 2 weeks prior to admission. Medical history included obstructive sleep apnoea and hypertension. His initial blood tests showed a mild hyperbilirubinaemia and acute kidney injury stage 1. Chest X-ray and CT pulmonary angiogram were negative for features suggestive of COVID-19. He later developed a drop in haemoglobin and repeat bloods showed markedly raised lactate dehydrogenase and positive direct antiglobulin test. These results were felt to be consistent with a haemolytic anaemia. A nasopharyngeal swab came back positive for COVID-19. We suspect the cause of his symptoms was an autoimmune haemolytic anaemia secondary to COVID-19 which has recently been described in European cohorts.

BACKGROUND

The current COVID-19 pandemic has exposed health staff to a new and potentially fatal disease. It was initially described in the Chinese province of Hubei and has rapidly spread throughout the world.¹ The current number of UK deaths is over 42 000.² As time goes on, we are becoming more aware of the complications of this new disease. This includes renal failure, thrombosis, cardiomyopathy and the recently describe 'long COVID-19'.³⁻⁶ There have been a few cases reports of autoimmune haemolytic anaemia (AIHA) associated with COVID-19.^{7,8} To the best of our knowledge, this is the first UK description of an AIHA associated with this viral infection. It is important to be aware that this is an atypical presentation of COVID-19 that may occur during the period of infectivity.

CASE PRESENTATION

A man in his early 50s was admitted feeling non-specifically unwell for 5 days. His family had noticed a yellow discoloration in his eyes. His urine was dark and he had an episode of frank per rectum (PR) bleeding. He described a previous episode of PR bleeding 6 months prior to admission. He had had one episode of diarrhoea. He had coryzal symptoms 2 weeks prior to admission and was experiencing some shortness of breath on mild exertion.

Medical history included obstructive sleep apnoea and hypertension. He was not on any medication on admission. He had struggled with side effects from bisoprolol and ramipril for his hypertension. He had been prescribed aspirin and atorvastatin but he had stopped these medications. His blood pressure had not required treatment since October 2019.

His clinical examination was unremarkable except for mild jaundice. PR did not show blood or melaena. His blood pressure was 173/104 mm Hg, heart rate 110 beats/min, temperature 36.4°C, respiratory rate 20/min and O₂ saturations 96% on room air.

INVESTIGATIONS

His initial blood tests are shown in [tables 1 and 2](#); abnormal results are in bold.

There was evidence of an acute kidney injury (AKI) stage 1 and raised bilirubin.

His ECG on admission showed sinus tachycardia with heart rate of 122 beats/min.

A urine dip was positive for protein and blood. Due to the abnormal renal function, raised blood pressure and positive urine dip, a vasculitic screen was performed. This was negative. In view of the presumed haemolysis, further investigations were performed as detailed below.

DIFFERENTIAL DIAGNOSIS

An AIHA was suspected because of symptomatic anaemia, evidence of ongoing haemolysis on the blood tests and a history of a viral infection. In addition, the history of reddish urine, a positive urine dipstick for blood and protein and AKI stage 1 on presentation could have been suggestive of acute pyelonephritis. Gilberts syndrome was considered because of the mild hyperbilirubinaemia on the initial blood tests and clinical suspicion of viral infection as suggested by his coryzal symptoms.

Given the other abnormalities found, a haemolytic anaemia was the most likely diagnosis.

TREATMENT

He was initially treated with intravenous fluids and his renal function recovered. No antibiotics were prescribed. For the first few days of his admission, haemoglobin (Hb) continued to fall before stabilising. There was no evidence of overt bleeding.

Our initial thoughts had been that he may have had an acute glomerulonephritis secondary to a streptococcal infection or that this was an early presentation of vasculitis. However, his renal function improved with intravenous fluids and his vasculitic profile came back as negative. Antistreptolysin titres (ASOT) were not performed. His shortness of breath was felt to be secondary to anaemia or secondary to a recent COVID-19 diagnosis. Haematology input was requested to investigate for the potential haemolytic anaemia.

On the third day of his admission, he developed a supraventricular tachycardia which responded to adenosine 6 mg. Bisoprolol was initiated following this with the patients agreement.



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Table 1 Blood results days 1–5

	Day 1	Day 2	Day 3	Day 4	Day 5	Comments
Hb, g/L	125	107	86	88	79	
WBC, $\times 10^9/L$	11.3	14.6				
Plt, $\times 10^9/L$	194	242				
Neutrophils, $\times 10^9/L$	7.11	7.88	7.77	6.19		
Lymphocytes, $\times 10^9/L$	2.99	4.94	5.74	2.98		
Urea, mmol/L	14.9	25.2	18.6	9.6	6.1	
Creatinine, mmol/L	93	141	105	73	80	
eGFR	81	49	70	>90		
Sodium, mmol/L	139					
Potassium, mmol/L	4.1					
CRP, mg/L		63	50	48		
Total bilirubin, $\mu\text{mol/L}$	134	120	60	40	27	
ALP, U/L	47	52	47			
ALT, U/L	24	24	21			
Albumin, g/L	41					
LDH, U/L			2377	2493	2134	

ALP, alkaline phosphatase; ALT, alanine aminotransferase; CRP, C reactive protein; eGFR, estimated Glomerular filtration rate; Hb, haemoglobin; LDH, lactate dehydrogenase; WCC, white cell count.

OUTCOME AND FOLLOW-UP

Over the following days, his clinical picture improved with intravenous fluids and simple analgesia. The Supraventricular tachycardia (SVT) was treated as above and the haematological investigations suggested a haemolytic anaemia. His blood pressure on discharge was 114/56 mm Hg. An outpatient flexible sigmoidoscopy was also organised to investigate the two episodes of PR bleeding.

His general practitioner kindly repeated his blood tests after discharge. Table 3 shows the improvement in Hb back towards baseline.

We suspect that this patient had haemolytic anaemia secondary to COVID-19 infection. This is suggested by a raised lactate dehydrogenase (LDH), decline in Hb, low haptoglobin levels and positive anti-C3d. ASOT were not performed as his symptoms could have been secondary to a streptococcal infection. However, the temporal relationship between the coryzal symptoms and the COVID-19 positive swab suggests that this infection was the precipitant of the haemolytic anaemia. A COVID-19 antibody test was not performed as it was not available at that time in the hospital.

Final diagnosis: AIHA secondary to COVID-19.

DISCUSSION

Our patient presented with a features suggestive of haemolysis with mild jaundice, anaemia and dark urine. AIHA is an acquired haemolysis in which the host's immune system attacks its own red cell antigens. The incidence reported is approximately 1 per 100 000/year. Serologically, cases are divided into warm, cold or mixed types.⁹ Patients may present with symptoms of anaemia such as dizziness, tiredness and dyspnoea, or evidence of haemolysis with jaundice and dark urine.¹⁰

Typical laboratory findings of AIHA are anaemia, which may be absent in cases of mild haemolysis. The white blood cells and platelets are usually normal but leucopenia or leucocytosis may be seen due to viral infection or a bone marrow disorder. On a blood film, red blood cell agglutination and spherocytosis may be apparent. The reticulocyte count is usually increased but may be normal in cases of a very short duration of haemolysis or with an underlying bone marrow disorder. LDH and bilirubin levels may be raised and haptoglobin levels may be reduced, as

Table 2 Additional investigations

CXR	Lungs and pleural recesses are clear. Normal mediastinal contours.			
CTPA	There is no large volume of ground-glass change, consolidation and no pleural fluid. There are no classical features of COVID-19.			
Blood film	Polychromasia. Rare basophilic stippling seen. Platelet anisocytosis with some large forms. Some neutrophil hypersegmentation			
Parvo virus	IgG positive, IgM negative			
Mycoplasma IgM	Negative			
COVID-19 PCR	Positive			
ANA	<400 weakly positive			Presumed false positive
ANCA	Negative			
Anti-GBM	Negative			
CK	85 U/L			
DAT	Anti-C3D positive 2+	Anti IgG negative	Anti IgA negative	All others negative
		Anti IgM negative	AntiC3c negative	
Reticulocyte count $\times 10^9/L$	124	206	259	306
Haptoglobin, g/L	<0.30		<0.30	
Urine PCR	Normal			
Ferritin, $\mu\text{g/L}$	2452		Acute phase reactant	
B12, ng/L	420			
Folate, $\mu\text{g/L}$	8.9			
G6PD, U/gHb	9.3			
Free kappa/lambda light chain ratio	26.97/26.60		No evidence of myeloma	
	1.01(normal)			

ANA, anti-nuclear antibody; ANCA, antineutrophil cytoplasmic antibody; CK, creatinine kinase; CTPA, CT pulmonary angiogram; CXR, chest X-Ray; DAT, direct antiglobulin test; GBM, glomerular basement membrane; G6PD, glucose-6-phosphate dehydrogenase; Hb, haemoglobin.

Table 3 Blood results day 9–35

	Day 9	Day 21	Day 35
Hb g/L	96	120	133
×10 ⁹ /L	8.84	8.14	9.18
Platelets ×10 ⁹ /L	315	263	238

Hb, haemoglobin.

here, however COVID-19 can also increase LDH levels which could affect the interpretation. If the direct antiglobulin test is positive, it indicates the presence of complement (C3d) attached to red blood cell membrane and immunoglobulins IgG, IgM, IgA.⁹ Urine dipstick may be positive for blood but negative for erythrocytes.

There are a number of causes of AIHA. These include autoimmune, viral, lymphoproliferative disorders and immunodeficiency states. In our patient, there was nothing to suggest malignancy and the resolution without any specific treatment makes an ongoing autoimmune cause less likely. Haemolysis secondary to viral infections is a common finding. Our patient also had negative mycoplasma IgM and negative parvo virus IgM both of which are common causes of cold AIHA. The PR bleeding had occurred before and was not felt to be relevant to his current presentation.

Two papers have previously described haemolysis secondary to COVID-19. The first paper describes a woman with underlying congenital thrombocytopenia who required steroids to treat her warm AIHA.⁷ The second paper describes seven patients who presented with symptomatic COVID-19 and developed signs of warm or cold haemolysis on average 9 days after admission. All required treatment with either steroids or transfusion.⁸

Our patient did not present with features typical of COVID-19, although he had coryzal symptoms 2 weeks before presentation.

Patient's perspective

Our patient kindly gave his permission to publish this case report but did not wish to make further comments.

Learning points

- ▶ Haemolytic anaemia may be a complication of COVID-19.
- ▶ It is important to be aware of late presentations so that patients who are potentially still infectious have appropriate infection control precautions.
- ▶ There may be other late manifestations of COVID-19 that become obvious as our experience of this disease increases.

Based on this history, a COVID-19 swab was sent which came back positive. The interpretation of this result could be contentious. While low rates of false positive tests are reported, there is evidence that PCR may remain positive for many weeks after infection. As this test is PCR based rather than based on viral culture, it is not possible to comment on whether the virus is viable or dead. It is therefore not clear how long people may remain infectious for after COVID-19.¹¹ An antibody test may have added additional evidence of a prior infection but it is also evident that some people who have had typical COVID-19 symptoms do not produce an antibody response.¹²

There was no other cause found that could explain the features of an AIHA. He did not require any specific treatment. Awareness should be maintained to identify possible presentations of COVID-19 complications.

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REFERENCES

- 1 WHO. Novel coronavirus – China, disease outbreak news, 2020. Available: <https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/>
- 2 GOV.UK coronavirus (COVID-19) in the UK. Available: <https://coronavirus.data.gov.uk/> [Accessed 29 Sep 2020].
- 3 Su H, Yang M, Wan C, *et al.* Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int* 2020;98:219–27.
- 4 Ruggeri M, Rodeghiero F. Thrombotic risk in patients with immune haemolytic anaemia. *Br J Haematol* 2016;172:144–6.
- 5 Arentz M, Yim E, Klaff L, *et al.* Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. *JAMA* 2020;323:1612–4.
- 6 Covid-19: What do we know about "long covid"? *BMJ* 2020;370.
- 7 Lopez C, Kim J, Pandey A, Huang T, DeLoughery TG. simultaneous onset of COVID-19 and autoimmune hemolytic anemia. *Br J Haematol* 2020.
- 8 Lazarian G, Quinquenel A, Bellal M, *et al.* Autoimmune haemolytic anaemia associated with COVID-19 infection. *Br J Haematol* 2020;190:29–31.
- 9 Hill QA, Stamps R, Massey E, *et al.* The diagnosis and management of primary autoimmune haemolytic anaemia. *Br J Haematol* 2017;176:395–411.
- 10 Warm autoimmune haemolytic anaemia in adults, evaluation and diagnosis.
- 11 Cheng H-Y, Jian S-W, Liu D-P, *et al.* Contact tracing assessment of COVID-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. *JAMA Intern Med* 2020. doi:10.1001/jamainternmed.2020.2020. [Epub ahead of print: 01 May 2020].
- 12 Fill Malfertheiner S, Brandstetter S, Roth S, *et al.* Immune response to SARS-CoV-2 in health care workers following a COVID-19 outbreak: a prospective longitudinal study. *J Clin Virol* 2020;130:104575.

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