Severe refractory warm autoimmune haemolytic anaemia after the SARS-CoV-2 Pfizer-BioNTech vaccine (BNT162b2 mRNA) managed with emergency splenectomy and complement inhibition with eculizumab

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SUMMARY
A male in his teens with a history of liver transplant for biliary atresia (aged 2 years) and autoimmune haemolytic anaemia (AIHA, aged 6 years) presented with jaundice, dark urine, fatigue and chest discomfort that began 48 hours after the first dose of SARS-CoV-2 Pfizer-BioNTech vaccine (BNT162b2 mRNA). Investigations revealed a warm AIHA picture. Over 4 weeks the patient developed life-threatening anaemia culminating in haemoglobin of 35 g/L (after transfusion), lactate dehydrogenase of 1293 units/L and bilirubin of 228 µmol/L, refractory to standard treatment with corticosteroids and rituximab. An emergency splenectomy was performed that slowed haemolysis but did not completely ameliorate it. Eculizumab, a terminal complement pathway inhibitor, was initiated to arrest intravascular haemolysis and showed a favourable response. AIHA is rare but described after the SARS-CoV-2 Pfizer-BioNTech vaccine. This case highlights the rare complication of AIHA, the use of emergency splenectomy for disease control, and the use of eculizumab.

BACKGROUND
Autoimmune haemolytic anaemia (AIHA) is an immune-driven destruction of erythrocytes.1 It is relatively uncommon, with an incidence of up to 3 per 100 000 per year,2 but its course can be severe. Although the pathogenesis is complex and heterogeneous, it is broadly categorised into two serological types: warm AIHA (wAIHA) and cold AIHA (cAIHA). In wAIHA, IgG antibodies bind to red blood cells (RBCs), with the highest affinity at 37°C, and cause extravascular haemolysis mediated mainly by splenic macrophages. In contrast, cAIHA is thought to arise from intravascular haemolysis by IgM binding, the optimum temperature being 0–4°C, and activation of the classical complement pathway.3 The first-line treatment of wAIHA is prednisolone, with dose tapering in those responsive after 2–3 weeks. If refractory then rituximab can be considered.3 Third-line treatments include splenectomy and immunosuppressants such as cyclophosphamide, mycophenolate mofetil (MMF), bortezomib and azathioprine. In life-threatening cases, intravenous immunoglobulin (IVIG) or plasma exchange can be used. Patients refractory to these standard lines of therapy have a poor prognosis,2 so novel approaches are important to explore.

CASE PRESENTATION
A male in his teens was admitted to a district general hospital (DGH) with a week history of dark urine, fatigue, palpitations, dizziness, dyspnoea on exertion and chest discomfort. Forty-eight hours prior to his presentation he had received the first dose of SARS-CoV-2 Pfizer-BioNTech mRNA vaccine (BNT162b2 mRNA). No feverish illness, change in dietary habit, vomiting, loose stool or change in medications prior to the event was noted. The medical history was significant with a liver transplant aged 2 years for biliary atresia, for which he received tacrolimus and prednisolone. A previous episode of AIHA aged 6 years was managed with corticosteroids, rituximab and a switch of tacrolimus to MMF for a limited period of time. Other long-standing medications included omeprazole, folic acid, fluticasone and clobetasone ointment.

INVESTIGATIONS
Initially on admission (day 1) to the DGH, laboratory tests revealed haemoglobin (Hb) of 70 g/L (reference range 130–166 g/L) and bilirubin of 98 µmol/L (reference range 0–20 µmol/L). This was treated as an AIHA picture and the patient initially responded to standard treatment (prednisolone 1 mg/kg, 60 mg once daily, tapered to 50 mg after 2 weeks). By day 26 the patient deteriorated with Hb of 82 g/L, bilirubin 147 µmol/L, lactate dehydrogenase (LD) 215–368 units/L and reticulocytes 220 × 10^9/L (reference range 25–105 × 10^9/L). Considering the history of steroid-resistant AIHA, second-line rituximab was started at 375 mg/m² and prednisolone increased back to 60 mg. Hb fell to 60 g/L by day 28, requiring 2 units of packed red blood cells (PRBC). The patient continued to haemolyse such that by day 29 the patient had become critically ill, with Hb of 35 g/L and LD of 1293 U/L. Figure 1 shows Hb concentration from day 29 of the admission and the number of PRBC units required. This necessitated an immediate transfer from the DGH to our tertiary centre for specialist support. Here, 4 units of PRBC were transfused alongside 100 mg methylprednisolone and 1 g/kg IVIG, folic acid and...
omепразол. The peripheral blood film showed severe anaemia, nucleated red cells, spherocytes, rouleaux, polychromasia, occasional tear drop poikilocytosis, anisocytosis and thrombocytopaenia. No autoagglutination, schistocytes or platelet clumps were seen. Haptoglobin was <0.1 g/L (reference range 0.5–2.6 g/L). Direct antiglobulin test (DAT) was positive for IgG (4+) and negative for C3d. Thrombocytopaenia (platelets 49 × 10^9/L, reference 150–370 × 10^9/L) was present; however, the creatinine and coagulation screen were normal. A CT showed splenomegaly of 15.5 cm and no lymphadenopathy. Urinalysis found urobilinogen and bilirubin at high concentrations, and urinary haemosiderin (a product of long-standing intravascular haemolysis) was negative.

DIFFERENTIAL DIAGNOSIS
Differential diagnoses were considered in light of the thrombocytopaenia. Heparin-induced thrombocytopaenia and paroxysmal nocturnal haemoglobinuria (PNH) screens were negative, a PLASMIC score for thrombotic thrombocytopaenia was 3 (thus at low risk), and the lack of schistocytes on repeated films and negative blood cultures made other microangiopathic haemolytic anaemias less likely.4 HIV and hepatitis serology were negative, as were adenosivirus, cytomegalovirus and Epstein-Barr virus PCR assays. Liver biochemistry was mildly abnormal but felt most consistent with systemic illness (and subsequent liver biopsy during the admission showed no immune infiltrate/rejection process). The investigations were consistent with wAIHA: a haemolytic picture on bloods (normocytic anaemia, reticulocytosis, high LD, hyperbilirubinaemia and low haptoglobin), the strongly positive IgG DAT and splenomegaly. cAIHA was unlikely due to a negative C3 on DAT.

TREATMENT
Despite the multiunit RBC transfusion and escalated treatment, in the early hours of day 30 the patient deteriorated: Hb had only increased to 54 g/L, bilirubin was elevated at around 200 μmol/L, and LD was rising as shown in figure 2. Considering this life-threatening fulminant haemolysis, refractiveness to current treatment and continued requirement for transfusions, in the morning of day 30 the decision was made to perform an emergency splenectomy as medical therapy (including consideration of plasma exchange) would be too slow to act. Three units of PRBC and 1 unit of platelets were transfused intraoperatively. The patient stabilised postoperatively: Hb increased to 83 g/L and bilirubin levelled to around 90 μmol/L. LD increased but began to trend slowly downwards in the following days. Despite the splenectomy, Hb continued to fall and the patient still required transfusions. A non-haemolytic cause of anaemia such as an acute bleed in the surgical site was considered so the patient was returned to theatre for haemostasis. This identified an active bleeding site from the abdominal wall in the drain hole, yet after repair the patient continued to haemolyse, requiring daily transfusions to maintain Hb >70 g/L. Lactate and bilirubin were still raised, although stable, and reticulocyte count was increasing. By day 33, the patient had received 15 units of PRBC. Histology of the spleen demonstrated erythrophagocytosis, red pulp congestion and extramedullary haemopoiesis.

There was some clinical suspicion that the patient was haemolysing intravascularly, as urine was on occasion coca-cola coloured and the patient experienced back pain during transfusions (with red urine immediately after). At no point were alloantibodies identified on transfusion samples. The symptoms experienced after transfusion were attributed to acute intravascular haemolysis from wAIHA-associated complement activation. Since the hospital had compassionate approval to use eculizumab if required, the decision was made to start eculizumab 900 mg once weekly on day 33 alongside rituximab, prednisolone 40 mg daily, repeat IVIG 1 g/kg, tacrolimus 2 mg twice per day and antibiotic cover with intravenous tazocin 4.5 g to switch to oral ciprofloxacin on stepdown. Post eculizumab the patient required less frequent transfusions, apart from one episode on the evening of day 34 where 4 units of RBC were required.

Further treatment alterations were made to optimise the haemoglobin. On day 35 MMF 500 mg two times per day was prescribed, and on day 36 tacrolimus was switched to ciclosporin 100 mg two times per day to rule out additional drug-induced haemolysis. Adjustments to immunosuppression were made after consensus agreement between hepatology and haematology services.

From day 36 onwards the haemolysis appeared to settle. By day 43 Hb was fluctuating around 70 g/L but was static, so the patient was discharged with appropriate follow-up and two times per week blood test monitoring. Further doses of eculizumab were given on days 40, 46, 54, 61, 75 and 83. Subsequent doses of rituximab were on day 40 and 46.

After this discharge the patient’s clinical status improved greatly. There were fewer episodes requiring RBC transfusions with longer intervals between them, for example, a further unit on days 50 and 52. In total during this admission he received 24 units of PRBCs. Fastidious attention to thromboprophylaxis was also made.

OUTCOME AND FOLLOW-UP
After day 50 Hb gradually increased and haemolysis plateaued. LD, bilirubin and reticulocytes followed a similar trend of a gradual decline after day 50 and normalised at day 59. A total of 7 doses of eculizumab were given. By the sixth eculizumab dose,
day 75, an acceptable haematological response was achieved: Hb
was 110 g/L, LD 246 units/L, bilirubin 20 µmol/L and reticu-
locytes were 116.6 × 10⁹/L, indicating the absence of haemolysis.

Treatment was complicated by raised ferritin and hepatic, but
not cardiac, iron overload—a common complication of large
volume transfusions. For this the patient was initiated on a vene-
section programme.

The patient was also referred to immunology to assess for
vaccination responses. IgG antibodies were identified against
SARS-CoV-2 and he had no history of infection. Other positive
findings included antibodies to tetanus, mumps and rubella. Anti-
body response was suboptimal for haemophilus, intermediate
for pneumococcal serotypes and there were none for measles.

DISCUSSION

Our case was interesting for multiple reasons. First, the haemo-
lysis was temporally related to the first dose of the SARS-
CoV-2 Pfizer-BioNTech vaccine. Similar associations have been
reported with acute COVID-19 infections and this vaccine,3–10
but were not refractory to standard treatment. It is proposed
that the SARS-CoV-2 spike protein subunits 1 and 2 activate
the alternative complement pathway,11 and in this case the lack
of COVID-19 symptoms, undetectable SARS-CoV-2 RNA on
repeat testing throughout the admission, and temporal proximity
to the vaccine suggest that the vaccine, not an acute infection,
was the cause.

Second, the emergency splenectomy (although scarcely used)
alongside PRBC transfusions was critical to stabilise the fulmi-
nant haemolysis and to allow time for pharmacological agents to
work. Since wAIHA is predominantly mediated by phagocytosis of
IgG coated RBCs by macrophages in the reticuloendothelial
system of the spleen, although irreversible the splenectomy was
the fastest therapeutic solution to the refractory haemolysis.
Postsplenectomy, Hb increased from 35 to 83 g/L, and in the
following days prior to eculizumab the haemolysis rate and clin-
ic picture settled enough to be managed by daily transfusions
of progressively smaller quantity.

Finally, eculizumab appeared to slow haemolysis sufficiently to
allow time for rituximab and MMF to act (median response time
of 3–6 weeks and 3–4 months, respectively).12 Eculizumab is a
monoclonal antibody targeting C5 of the complement cascade
to prevent activation of the membrane attack complex.13 In line
with the pathophysiology of wAIHA, one may expect comple-
ment inhibition to be less significant in this case. Although only
licensed for PNH and atypical haemolytic uraemic syndrome,
there have been previous case reports on the successful off-
licence use of eculizumab in wAIHA.14–19 There is evidence that
complement plays a role in wAIHA, as up to 50% of the DATs
in wAIHA are positive for complement fragments and some
IgG subclasses are able to activate complement via the classical
pathway.20 21

The improvement with eculizumab suggested that complement-
driven haemolysis was occurring. The question remains as to
whether this was intravascular or not, and there was conflicting
clinical evidence. In favour of an intravascular aetiology was
that although life-saving the splenectomy did not appear to
completely arrest haemolysis, and that the patient had coca-cola
coloured urine and experienced back pain during transfusions
(which are documented clinical sequelae of intravascular haemo-
lysis).22 Contrary to this, the patient had an IgG+C3d-DAT and
negative urinary haemosiderin, suggesting its absence.23 One
possible source of extravascular haemolysis could be the liver,
as Kupffer cells in the liver are able to phagocytose C3b-opsonised
erthrocytes.24

Patient’s perspective

The sudden rate at which my condition deteriorated was
incredibly alarming and was a real shock to the system when,
in the space of less than a few days I had gone from living
a fairly normal life (aside from the occasional liver-related
appointment), to being bed-ridden and unable to stand without
feeling incredibly nauseous. The team were incredible in jumping
into action as soon as I arrived at the hospital and continued to
throw the best treatment they had at me, until I had made a full
recovery. Initially, post splenectomy, the haemoglobin was stable
but still far below what it needed to be. This made anything
more than merely standing up too much to sustain. Additionally
to this, the splenectomy meant that any type of movement
(even within the bed) was incredibly tough. Thankfully, after a
few transfusions to keep the level stable while the treatment
got to work, the numbers quickly started to come up. However,
this was several weeks after the first admission and so by this
point I was on a very high dose of steroids and had received
multiple sessions of blood transfusion. As a result, I was put
on a programme to slowly reduce the levels of steroid and
had approximately a dozen venesections to lower iron levels
across a period of a couple of months. My condition is now
overall stable. I have returned to school and all other previous
sports commitments and am slowly reducing levels of MMF, in
accordance with the liver team.

Learning points

► Emergency splenectomy may be life-saving for severe acute
autoimmune haemolytic anaemia.
► Autoimmune haemolytic anaemia is a rare complication of
COVID-19 vaccines.
► This report adds to the literature of eculizumab utility in
autoimmune haemolytic anaemia.

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