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) 597 units/L (reference range 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/m^2 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

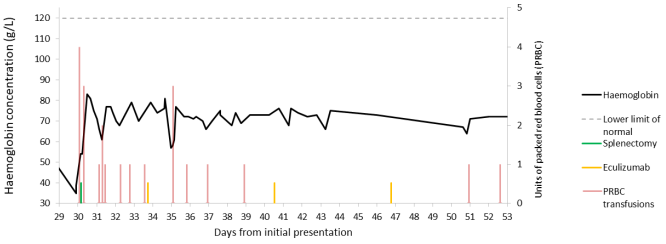

Figure 1 Haemoglobin concentration from day 29 of admission to day 53 shown as a black line. Units of packed red blood cells (PRBC) transfused shown as red vertical lines, proportional to number of units. Timing of splenectomy shown as a green vertical line. Eculizumab doses shown as yellow vertical lines.

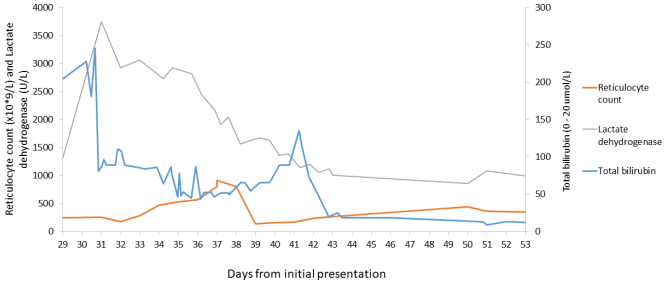

Figure 2 Bilirubin, lactate dehydrogenase and reticulocyte count from day 29 of admission until day 53, shown as blue, grey and orange lines, respectively.

omeprazole. The peripheral blood film showed severe anaemia, nucleated red cells, spherocytes, rouleaux, polychromasia, occasional teardrop 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 adenovirus, 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 erythophagocytosis, red pulp congestion and extramedullary haematopoiesis.

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 two times 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 reticulocytes were 116.6 × 10^9/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 venesection 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. Antibody 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 haemolysis 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,[5–10] 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 fulminant 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 clinical 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 complement 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 sequalae of intravascular haemolysis).[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 erythrocytes.[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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REFERENCES

1 Barcellini W, Fattizzo B. The changing landscape of autoimmune hemolytic anemia. *Front Immunol* 2020;11:946.
2 Barcellini W, Fattizzo B, Zaninoni A, *et al*. Clinical heterogeneity and predictors of outcome in primary autoimmune hemolytic anemia: a GIMEMA study of 308 patients. *Blood* 2014;124:2930–6.
3 Berentsen S, Barcellini W. Autoimmune hemolytic anemias. *N Engl J Med* 2021;385:1407–19.

4 Bendapudi PK, Hurwitz S, Fry A, *et al*. Derivation and external validation of the plasmic score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. *Lancet Haematol* 2017;4:e157–64.
5 Capes A, Bailly S, Hantson P, *et al*. COVID-19 infection associated with autoimmune hemolytic anemia. *Ann Hematol* 2020;99:1679–80.
6 Lazarian G, Quinquenel A, Bellal M, *et al*. Autoimmune haemolytic anaemia associated with COVID-19 infection. *Br J Haematol* 2020;190:29–31.
7 Hindilerden F, Yonal-Hindilerden I, Akar E, *et al*. Severe autoimmune hemolytic anemia in COVID-19 İnfection, safely treated with steroids. *Mediterr J Hematol Infect Dis* 2020;12:e2020053.
8 Lopez C, Kim J, Pandey A, *et al*. Simultaneous onset of COVID-19 and autoimmune haemolytic anaemia. *Br J Haematol* 2020;190:31–2.
9 Pérez-Lamas L, Moreno-Jiménez G, Tenorio-Núñez MC, *et al*. Hemolytic crisis due to Covid-19 vaccination in a woman with cold agglutinin disease. *Am J Hematol* 2021;96:E288–91.
10 Murdych TM. A case of severe autoimmune hemolytic anemia after a receipt of a first dose of SARS-CoV-2 vaccine. *Int J Lab Hematol* 2022;44:e10-e12.
11 Yu J, Yuan X, Chen H, *et al*. Direct activation of the alternative complement pathway by SARS-CoV-2 spike proteins is blocked by factor D inhibition. *Blood* 2020;136:2080–9.
12 Hill QA, Stamps R, Massey E, *et al*. The diagnosis and management of primary autoimmune haemolytic anaemia. *Br J Haematol* 2017;176:395–411.
13 Patriquin CJ, Kuo KHM, Eculizumab KKHM. Eculizumab and beyond: the past, present, and future of complement therapeutics. *Transfus Med Rev* 2019;33:256–65.
14 Hillmen P, Young NS, Schubert J, *et al*. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med* 2006;355:1233–43.
15 Legendre CM, Licht C, Muus P. Terminal complement inhibitor eculizumab in atypical hemolytic–uremic syndrome. *N Engl J Med* 2013.
16 Neave L, Wilson AJ, Lissack M, *et al*. Severe refractory idiopathic warm autoimmune haemolytic anaemia responsive to complement inhibition with eculizumab. *BMJ Case Rep* 2018;11:e226429.
17 Gauchy A-C, Hentzien M, Wynckel A, *et al*. Efficacy of eculizumab in refractory life-threatening warm autoimmune hemolytic anemia associated with chronic myelomonocytic leukemia. *Clin Case Rep* 2020;8:2641–4.
18 Ma K, Caplan S. Refractory IgG warm autoimmune hemolytic anemia treated with eculizumab: a novel application of anticomplement therapy. *Case Rep Hematol* 2016;2016:1–3.
19 Chao MP, Hong J, Kunder C, *et al*. Refractory warm IgM-mediated autoimmune hemolytic anemia associated with churg-strauss syndrome responsive to eculizumab and rituximab. *Am J Hematol* 2015;90:78–81.
20 Li Z, Shao Z, Xu Y, *et al*. Subclasses of warm autoantibody IgG in patients with autoimmune hemolytic anemia and their clinical implications. *Chin Med J* 1999;112:805–8.
21 Barcellini W. New insights in the pathogenesis of autoimmune hemolytic anemia. *Transfus Med Hemother* 2015;42:287–93.
22 Rother RP, Bell L, Hillmen P, *et al*. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. *JAMA* 2005;293:1653–62.
23 Barcellini W, Fattizzo B. Clinical applications of hemolytic markers in the differential diagnosis and management of hemolytic anemia. *Dis Markers* 2015;2015:e635670
24 Berentsen S, Sundic T. Red blood cell destruction in autoimmune hemolytic anemia: role of complement and potential new targets for therapy. *Biomed Res Int* 2015;2015:1–11.