Refractory severe immune thrombocytopenia in a twin pregnancy

Patrick Harrington¹, Catherine Nelson-Piercy¹,
Catherine Williamson², Nichola Cooper³, Rachel Kesse-Adu¹ and
Susan Robinson¹

Abstract

A 34-year-old woman presented at 29 weeks gestation of a twin pregnancy, with a platelet count of $1 \times 10^9/l$. She was extensively investigated and was subsequently diagnosed with severe immune thrombocytopenia. She did not respond to initial treatment with corticosteroids and intravenous immunoglobulin. She also failed to respond to second-line therapies of Anti-D immunoglobulin, Azathioprine and the thrombopoietin agonist Romiplostim. Her case was further complicated by an episode of obstetric cholestasis possibly related to Azathioprine treatment. She went on to require plasma exchange around the time of an elective Caesarean section which provided temporary improvement in the platelet count and enabled safe delivery. This case highlights some of the challenges faced in the management of patients with severe and refractory immune thrombocytopenia during pregnancy.

Keywords

Haematology, high-risk pregnancy, immunology, multiple pregnancy

Date received: 1 February 2017; accepted: 30 March 2017

A 34-year-old primiparous woman presented at 29 weeks gestation of a dichorionic, diamniotic twin pregnancy to her local hospital, complaining of a widespread rash, blisters in her mouth and red urine. Obstetric history included two previous first trimester miscarriages and there was no other medical history of note. Ten days prior to presentation, she had received the seasonal influenza vaccine. She denied any previous bleeding or bruising symptoms. Full blood count (FBC) at booking was normal.

On initial assessment, there was evidence of a diffuse petechial rash and several discrete mucosal ecchymoses. Clinical examination was otherwise unremarkable. She was normotensive and urinalysis excluded significant proteinuria but confirmed haematuria. Routine blood tests were performed including an FBC which identified an isolated thrombocytopenia with a platelet count of $1 \times 10^9/l$. Blood film examination was unremarkable other than confirming severe thrombocytopenia. Liver enzymes and functions (LFTs) were at this stage within normal limits.

The provisional diagnosis was immune thrombocytopenia (ITP). In view of her haematuria, she received one adult therapeutic dose of platelets, and commenced Prednisolone 1 mg/kg and a course of intravenous immunoglobulins (IVIg) 0.4 g/kg daily was given over five days. After the completion of this treatment, there was an initial improvement in the platelet count, which had increased to $12 \times 10^9/l$, and she was discharged after six days with a plan for close monitoring. She was investigated extensively following initial presentation with no alternative cause for the thrombocytopenia found (Appendix 1).

Ten days after her initial presentation, she was readmitted due to a fall in the platelet count to $7 \times 10^9/l$. She was asymptomatic at this point but was noted to have a mild transaminitis with an alanine transferase (ALT) of 76 IU/l. By day 12, the platelet count had fallen further to $1 \times 10^9/l$, and following discussion with a tertiary unit, a further dose of IVIg was given with minimal effect. A bone marrow aspirate and trephine demonstrated megakaryocytic hyperplasia, consistent with a diagnosis of immune thrombocytopenia. Immunophenotyping was also performed and excluded a clonal disorder. The patient was subsequently transferred to our centre for further management.

Treatment options were discussed with the patient who was not keen on proceeding with Rituximab or Cyclosporine. Off license treatment with intravenous Anti-D immunoglobulin was then considered

(blood group Rh D positive and direct antiglobulin test (DAT) was negative). An intravenous dose of 250 IU/kg was well tolerated. However, four days following administration, the platelet count remained $3 \times 10^9/l$. Due to the severity of thrombocytopenia and lack of response to Anti-D, immunosuppressive therapy with Azathioprine was commenced, after confirming a normal thiopurine methyltransferase (TPMT) level. This was started at a dose of 50 mg daily and escalated to 100 mg daily a few days later. LFTs at this point showed a stable mild transaminitis with an ALT of 86 IU/l and a normal alkaline phosphatase (ALP).

In view of the relatively slow onset of action of Azathioprine, ongoing severe thrombocytopenia and advanced gestation of 32 weeks, it was felt necessary to attempt to optimise the platelet count in anticipation of delivery. A single dose of Romiplostim, 2 mcg/kg, was given six days after initiation of Azathioprine following review of current literature on the use of thrombopoietin analogues in pregnancy (see Discussion). Over the subsequent week, a progressive transaminitis was noted with the ALT rising to 621 IU/l. Bile acids were also elevated at $97 \mu\text{mol/l}$, and a provisional diagnosis of intra-hepatic cholestasis of pregnancy (ICP) was made, and the patient was started on Ursodeoxycholic acid. Azathioprine treatment had been discontinued due to the progression of the transaminitis and no further Romiplostim was administered during pregnancy. Following this, the liver function gradually improved, returning to normal over approximately two weeks.

There had been no improvement in the thrombocytopenia and so it was decided to initiate therapeutic plasma exchange at 34 weeks. Over the following 10-day period, seven single-plasma volume exchanges

¹Guys and St Thomas' NHS Foundation Trust, Guys Hospital, London, UK

²King's College London, London, UK

³Imperial College NHS Trust, London, UK

Corresponding author:

Patrick Harrington, Haematology Offices, 4th Floor Southwark Wing, Guys Hospital, Great Maze Pond, London SE1 9RT, UK.

Email: Patrick.harrington@gstt.nhs.uk

were performed using solvent detergent fresh frozen plasma (FFP). This was well tolerated and no complications were noted. Following the completion of the final plasma exchange, further treatment was given with IVIg at a dose of 1 g/kg on consecutive days. There were transient responses to plasma exchange with the platelet count improving to a maximal level of $37 \times 10^9/l$; however, this was not sustained.

The following day, an elective Caesarean section under general anaesthetic was performed. Intravenous Tranexamic acid, at a dose of 1 g, was administered and one therapeutic dose of platelets was transfused prior to the first incision, with a further dose given

intra-operatively. A single unit of packed red cells was also given intra-operatively. Intra-operative platelet count was $79 \times 10^9/l$. There was an estimated blood loss of 1700 ml during the procedure and intravenous iron was given to correct post-operative anaemia. Of note, both neonates were also found to have severe thrombocytopenia with nadir platelet counts of less than $20 \times 10^9/l$, and as such both were treated with IVIg at a dose of 0.4 g/kg over five days.

Over the next five days, a further three pooled units of platelets were transfused to maintain a level of greater than $50 \times 10^9/l$ to prevent haematoma formation, and thromboprophylaxis was also administered in view of the postnatal thrombotic risk. Unfortunately, in the post-natal period, the patient has remained severely thrombocytopenic and at the time of writing has failed to respond to a further trial of Romiplostim, as well as subsequent Rituximab therapy, at a dose of 375 mg/m^2 over four weeks. She is currently being treated with Mycophenolate Mofetil but is yet to respond adequately and as such is being considered for splenectomy.

Figure 1. CD61 stain of bone marrow trephine showing megakaryocyte hyperplasia.

Discussion

This case highlights some of the challenges seen in the management of patients with severe and refractory ITP during pregnancy. There is a need to optimise the platelet count to a safe level as pregnancy advances, to support the mode of delivery, facilitate regional analgesia and anaesthesia and minimise the risk of peripartum complications. In the first and second trimester, in the absence of symptoms or planned intervention, the international consensus report recommends treatment is initiated when the platelet count falls below $20\text{--}30 \times 10^9/l$ or in symptomatic patients.¹ There is limited literature regarding the use of second- and third-line treatments for ITP in pregnancy. The case also demonstrates the potential risk of placental transfer of maternal antibodies, which is estimated to cause severe neonatal thrombocytopenia in around 10% of pregnancies complicated by ITP.

Figure 2. ALT and platelet count over course of admission. ALT: alanine transferase.

Azathioprine is generally recognised as a safe and well-tolerated treatment in pregnancy, based on data from patients with SLE and renal transplants.² It is thought to be non-teratogenic as the fetus lacks the enzyme inosinotriphosphorylase, which is required to convert Azathioprine to the active metabolite 6-mercaptopurine.³ However, the time to onset of action with Azathioprine is normally estimated at six to eight weeks, limiting its use, particularly in the later stages of pregnancy.

The use of Anti-D immunoglobulin as a treatment for refractory ITP is becoming less common with the development of new treatments, but is an established and efficacious treatment for ITP, although it remains unlicensed.⁴ Anti-D given intravenously for ITP is given at a significantly higher dose, than is used commonly in obstetric practice to prevent sensitisation in Rh D negative females. There is a theoretical risk of inducing haemolytic disease of the new-born and close monitoring of haemolytic markers as well as a DAT is advised post-delivery. There is also a risk of inducing maternal intravascular haemolysis, which can be severe. Manufacturers advise inpatient monitoring for a period of 8 h, with regular urinalysis for haemoglobinuria and evaluation of FBC and serum haemolysis markers if detected. However, the data that are available suggest that Anti-D is safe for both mother and fetus in the second and third trimesters. A study looking at eight pregnant women with ITP, and a median pre-treatment platelet count of $28 \times 10^9/l$, demonstrated a response rate of 75% with intravenous Anti-D immunoglobulin.⁵ Another paper reported on a single case of a patient responding to IV Anti-D treatment after failing treatment with standard IVIg and corticosteroids.⁶

Plasma exchange is rarely used to treat ITP, although is an effective way to reduce circulating anti-platelet autoantibodies in emergency situations. One report described two cases of severe ITP successfully treated with plasma exchange to allow for emergency surgery to be performed.⁷ Plasma exchange, although invasive, is safe in pregnancy and commonly used in pregnant patients with other conditions. Rituximab is an IgG1 monoclonal antibody to CD20, which crosses the placenta and has shown teratogenicity in animal studies. As such it is preferable to avoid the use of Rituximab in pregnancy and indeed for 6–12 months prior to conception. However, in severe ITP that is refractory to alternative treatments, it can be considered as an exceptional approach in pregnancy. A study reported on 153 pregnancies involving maternal or paternal pre-conceptual Rituximab exposure, given for a range of underlying conditions, and in many cases with other potentially teratogenic medications.⁸ Of 90 live births there were only two incidences of congenital malformation (2.2%), suggesting that in certain cases the benefits of treatment to the mother outweigh potential risks to the fetus.

Thrombopoietin analogues are commonly used in patients with chronic ITP who are refractory to standard first-line therapies. There is a lack of evidence for their use in pregnancy and as such they are currently unlicensed in this setting; however, they may be particularly beneficial as a short-term measure to increase the platelet count around an expected delivery date. Three previous papers have reported on a total of four patients with chronic, refractory ITP who were successfully managed with Romiplostim.^{9–11} A previous study looking at thrombopoietin levels in normal pregnancy demonstrated levels twice as high as the non-pregnant control group, possibly suggesting that some patients may not respond to these agents during pregnancy.¹² Hepatotoxicity is a reported adverse effect of thrombopoietin agonists, particularly the orally administered agent Eltrombopag.¹³ However, it should be noted that these agents are licensed for use in patients with chronic thrombocytopenia secondary to severe pre-existing liver disease and are generally well tolerated.

The episode of cholestasis that occurred in conjunction with the elevated ALT resolved rapidly. The serum bile acid concentration was elevated to $97 \mu\text{mol/l}$ six days prior to the highest ALT measurement, and prior to treatment with Romiplostim, suggesting that the maternal cholestasis was either caused by treatment with Azathioprine or this

was pregnancy-induced cholestasis. ICP most commonly presents at 32 weeks' gestation, and biochemical impairment can respond to treatment with Ursodeoxycholic acid.^{14,15} In this case, the serum bile acids had reduced dramatically within six days and were $16 \mu\text{mol/l}$ on the day the ALT concentration was 621 IU/l . As most women with ICP do not have complete resolution of cholestasis until after delivery of the fetus and placenta, it is more likely that Azathioprine contributed to the cholestasis and marked elevation of liver transaminases and that cessation of this drug resulted in clinical and biochemical improvement. While Azathioprine-induced cholestasis has not been reported in pregnancy, it is occasionally seen in non-pregnant individuals. Furthermore, women with ICP have increased susceptibility to developing other forms of drug-induced cholestasis outside of pregnancy, e.g. secondary to ingestion of the combined oral contraceptive pill or antibiotics.¹⁶ Co-administration of Romiplostim and Azathioprine may have exacerbated the hepatocellular injury.

Despite the proximity of the onset of symptoms to receiving the influenza vaccine in this case, there is no convincing evidence to suggest that this was the cause of the patient's ITP, and as such adherence to the current vaccination schedule is advised.

This case demonstrates some of the difficulties faced in the management of patients with severe and refractory ITP. Whilst the majority of patients will respond to first-line treatment, some cases will be more challenging and require the use of second- and third-line therapies. It is important that future efforts focus on the efficacy of these agents in the pregnant population.

Acknowledgements

The authors would like to acknowledge the contribution of Dr M. Moonim, Histopathology Department, GSTT, for providing the histopathology image included in the article.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

Written patient consent was obtained.

Guarantor

PH.

Contributorship

PH wrote the article. All other authors reviewed and critically evaluated the article.

References

1. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010; 115: 168–186.
2. Price HV and Salaman JR. Immunosuppressive drugs and the foetus. *Transplantation* 1976; 21: 294–298.
3. Polifka JE and Friedman JM. Teratogen update: azathioprine and 6-mercaptopurine. *Teratology* 2002; 65: 240–261.
4. Newman GC, Novoa MV, Fodero EE, et al. A dose of 75 g/kg/d of i.v. anti-D increased the platelet count more rapidly and for a longer

period of time than 50 g/kg/d in adults with immune thrombocytopenic purpura. *Br J Haematol* 2001; 112: 1076–1078.

5. Michel M, Novoa MV, Bussel JB, et al. Intravenous anti-D as a treatment for immune thrombocytopenic purpura (ITP) during pregnancy. *Br J Haematol* 2003; 123: 142–146.
6. Sieunarine K, Shapiro S, Al Obaidi MJ, et al. Intravenous anti-D immunoglobulin in the treatment of resistant immune thrombocytopenic purpura in pregnancy. *BJOG* 2007; 114: 505–507.
7. Finn L and Tun H. Combined plasma exchange and platelet transfusion in immune-mediated thrombocytopenic emergencies. *Transfus Apher Sci* 2013; 49: 661–664.
8. Chakravarty E and Murray E. Pregnancy outcomes after maternal Rituximab exposure. *Blood* 2011; 117: 1499–1506.
9. Alkaabi JK and Alkindi S. Successful treatment of severe thrombocytopenia with romiplostim in a pregnant patient with systemic lupus erythematosus. *Lupus* 2012; 21: 1571–1574.
10. Decroocq J and Marcelin L. Rescue therapy with romiplostim for refractory primary immune thrombocytopenia during pregnancy. *Obstet Gynecol* 2014; 124: 481–483.
11. Giermasz A and Knoche J. Tolerability and efficacy of romiplostim as management of severe refractory immune thrombocytopenia (ITP) during pregnancy. *Thromb Haemost* 2013; S3: 75.
12. Frölich MA, Datta S and Corn SB. Thrombopoietin in normal pregnancy and preeclampsia. *Am J Obstet Gynecol* 1998; 179: 100–104.
13. Cuker A. Toxicities of the thrombopoietic growth factors. *Semin Haematol* 2010; 47: 289–298.
14. Geenes V, Chappell LC, Seed PT, et al. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population-based case-control study. *Hepatology* 2013; 59: 1482–1491.
15. Bacq Y, Sentilhes L, Reyes HB, Glantz A, et al. Efficacy of ursodeoxycholic acid in treating intrahepatic cholestasis of pregnancy: a meta-analysis. *Gastroenterology* 2012; 143: 1492–1501.
16. Dixon PH and Williamson C. The pathophysiology of intrahepatic cholestasis of pregnancy. *Clin Res Hepatol Gastroenterol* 2016; 40: 141–153.

Appendix I. Results of extended investigations.

HIV	Negative
Hep B sAg	Negative
Hep C Ab	Negative
CMV IgG/M	Negative
EBV IgM	Negative
ACL IgM	3.9 MPL U/ml
ACL IgG	2.7 GPL U/ml
Lupus AC	Not detected
vwF:RCO	>400%
vWF:Ag	>400%
FVIII	430%
ADAMTS13	119.8%
Folate	>20 µg/l
BI2	214 pmol/l
LDH	300 U/l
Retics	$81.2 \times 10^9/l$
Haptoglobin	1.05 g/l
DAT	Negative
ALT	76 IU/l
ALP	79 IU/l
Alb	34 g/l
Protein electrophoresis	Normal
ANA	Negative