Aplastic anaemia in pregnancy with severe thrombocytopenia refractory to platelet transfusion: a case and management plan

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Summary: Aplastic anaemia is a rare haematological disorder during pregnancy, which when complicated by severe thrombocytopenia poses a significant maternal risk. A woman with aplastic anaemia and a platelet (PLT) count of $11 \times 10^9/L$ refractory to PLT transfusion required caesarean delivery. Proactive planning by a multidisciplinary team, large volume PLT transfusion prior to surgery and postoperative uterine artery embolization resulted in avoidance of mortality. Maternal preferences should be discussed in detail due to the high risk of maternal morbidity and mortality associated with severe aplastic anaemia. This report outlines a management plan to address the medical and ethical issues faced when caring for a pregnant patient with severe aplastic anaemia and severe thrombocytopenia. We credit the good outcome to our proactive multidisciplinary approach.

Keywords: aplastic anaemia, pregnancy, platelet transfusion, refractory, thrombocytopenia

INTRODUCTION

Aplastic anaemia is a rare disorder characterized by pancytopenia and a hypocellular bone marrow. Causes include radiation exposure, drugs and chemicals, viral infections, pregnancy and 70% are idiopathic.^{1–8} While maternal mortality has been reported as 20–60%, we present a management plan for caesarean delivery in a woman whose pregnancy was complicated by aplastic anaemia and severe refractory thrombocytopenia.^{6–8}

CASE

Our patient is a G2 P1001 in her mid-20s. An extensive discussion with her paediatric haematologist revealed that Fanconi's anaemia, paroxysmal nocturnal haemoglobinuria and autoimmune and infectious aetiologies were excluded. Marrow biopsies at age nine and 16 were consistent with the diagnosis of acquired aplastic anaemia. Multiple medical treatments between 17 and 22 years of age, including IV IgG, cyclosporine, anti-thymocyte globulin and granulocyte macrophage colony stimulating factor (GM-CSF), failed to increase her platelet (PLT) count above $30 \times 10^9/L$. During her first pregnancy, the PLT count ranged from 10 to $30 \times 10^9/L$ and reticulocyte count 1.7%. Single-donor PLT transfusions were given to maintain PLT count $>15 \times 10^9/L$ (the arbitrary level agreed upon by

the care team). PLT antibodies were positive to HLA Class I antigens only, the usual cause for suspected PLT alloimmunization. After an uncomplicated vaginal delivery at 37 weeks gestation (PLT $16 \times 10^9/L$), she was discharged on postpartum day two with a PLT count of $21 \times 10^9/L$ and was advised to avoid pregnancy in the future. Six years later, she presented at eight weeks gestation (PLT $25 \times 10^9/L$) and was followed collaboratively by maternal-fetal medicine, obstetric medicine, critical care medicine, haematology and interventional radiology. Laboratory values, transfusion history and the response to transfusions are listed in Table 1. HIV antibody was negative, PT/aPTT were normal and no new PLT antibodies were detected. At 26 weeks, the third episode of epistaxis was treated with PLT transfusion and a two-week trial of oral prednisone 60 mg/day for possible superimposed immune thrombocytopenia (ITP), without an increase of the PLT count. Due to prior allergic reactions and the lack of a response in the past, the haematologist decided not to administer IV IgG. At 33 weeks, in response to a PLT count of $9 \times 10^9/L$, two units of single-donor PLTs were transfused without a response supporting refractoriness to PLT transfusion secondary to anti-HLA alloimmunity. An attempted marrow aspirate resulted in a dry tap. Her case was presented at the monthly OB Critical Care committee meeting and a plan outlined to minimize the risk of fatal maternal haemorrhage during delivery. Issues were proactively identified and the following treatment guidelines reached after discussions with the patient:

- (1) An advance directive incorporating the mother's wishes was written and approved by our ethics committee. When stable, the mother would be the primary patient

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Table 1 Platelet count, haemoglobin and response to transfusion of a pregnant patient with aplastic anaemia*

Date	Gestational age (weeks)	Laboratory Value Pre-transfusion			Number of Units Transfused			Laboratory Value Post-transfusion			Comment	
		PLT	Hgb	Fibrinogen	PLT	Packed Red Cell	Cryo	FFP	PLT	Hgb		Fibrinogen
Unit		×10 ⁹ /L	g/dL	mg/dL					×10 ⁹ /L	g/dL	mg/dL	WBC ×10 ⁹ PT/aPTT = seconds
Pregnancy 1	31.5	10	10.7		2							Crossmatched Delivery 1
Pregnancy 1	33.2	13	10.8		2							
Pregnancy 1	34.2				1				17	10.9		
Pregnancy 1	37	16	11.6		1				29	9.6		
Pregnancy 2	8	25										
Pregnancy 2	23	19	8.5		1				14			
Pregnancy 2	25.4	12	8.5		1				10	8.2		
Pregnancy 2	26.1	10	7.6		1	1			15	8.6		
Pregnancy 2	26.2		8			1			10	10		
Pregnancy 2	26.6	8	9.2		1				12	9		
Pregnancy 2	27.3	12	9.5		1				13	9		
Pregnancy 2	27.4	13	9		1				13	8.7		
Pregnancy 2	33	11	8.1		1				9	7.3		
Pregnancy 2	33.1	9	7.3		2				11	7.2		
Pregnancy 2	33.2		7.3			2				7.2		
Pregnancy 2	33.3		8.8			2				10.7		WBC 5.0
Pregnancy 2	41.4	11	9.8	199	10	3	10	8				WBC 3.3, 54% Neutrophils, PT 11, aPTT 27
Intoperatively												WBC 2.2
Pregnancy 2	41.4				6	7	10		124	10.8	276	
Postoperatively												
Pregnancy 2	POD 1	124	6.9	245	3	3			75	8.2	280	WBC 4.9 PT 11.7, aPTT 25.1
Pregnancy 2	POD 2	50	7.1	444	1	2	10		39	8.3		WBC 5.7 PT 12, aPTT 28.9
Pregnancy 2	–	39	8.3	516	1				68	9.1		WBC 6.3 PT 11.8, aPTT 28.3
Pregnancy 2	POD 3	44								8.1		WBC 4.8
Pregnancy 2	–	35								9.6		WBC 3.5
Pregnancy 2	POD 4		6.3			1				11		WBC 3.7
Pregnancy 2	POD 5	13	6.3		2	1			83	11		WBC 3.7
Pregnancy 2	POD 6	28	9.9	438								

Cryo = cryoprecipitate, FFP = fresh frozen plasma, Hgb = haemoglobin, PLT = platelet, POD = postop day, PT = prothrombin time, aPTT = activated partial thromboplastin time, WBC = white blood cell count
 *All platelet and packed red blood cell units were leukoreduced and irradiated

and caesarean birth would be avoided. If she became unstable (e.g. refractory life-threatening bleeding), then all attempts would be made to save her unborn child;

- (2) Fetal monitoring would be performed to determine the need for fetal resuscitation, but caesarean section would not be performed for fetal distress;
- (3) As conduction anaesthesia was contraindicated, intrapartum analgesia would be provided using fentanyl via a patient-controlled IV pump;
- (4) If caesarean section became necessary, central venous access would be obtained as a preliminary procedure and general anaesthesia would be used;
- (5) Typically a unit of PLTs will increase the count by $10\text{--}20 \times 10^9/\text{L}$. Given her refractoriness, it was decided that to overcome the PLT alloimmunization, 10 units of single-donor PLTs would be given as the surgery commenced (goal being PLT count $>50 \times 10^9/\text{L}$).⁹ Even if the PLT count did not increase, the PLTs might have time to be activated and used for haemostasis before they were cleared by the immune system;
- (6) As marrow transplant is the ultimate treatment for aplastic anaemia, cord blood would be harvested should the technology become available to use it to treat the mother's disease.

She presented at 41 4/7 weeks in early labour. Ultrasound revealed polyhydramnios, an AFI of 34.4 cm and an estimated fetal weight of 4053 g. Despite pitocin stimulation and adequate contractions on internal monitoring, an arrest of active phase at 6 cm dilatation necessitated discussion of caesarean delivery to which the patient consented. The protocol listed above was followed. A vertical incision was used for better haemostasis and greater surgical exposure. Based on persistent oozing during the procedure, and the surgeons estimate of the amount of blood lost, she received the intraoperative blood products as listed in Table 1. The estimated blood loss was 1200 cc, and there was some generalized oozing without any identifiable bleeding points. The fascial incision was closed and the wound was left open and packed. She was transferred to the medical intensive care unit (MICU) intubated and in stable condition. As the haemoglobin actually increased from 9.8 g/dL preoperatively to 10.8 g/dL postoperatively, no further packed red blood cells (PRBCs) were transfused that day. In the MICU, furosemide was given for pulmonary oedema, her abdomen was distended and tender, vital signs were stable and PLT count was $124 \times 10^9/\text{L}$. Ultrasound revealed intra-abdominal fluid, presumably blood, so the patient was taken to the interventional radiology suite. While no arterial bleeding was noted at the time of bilateral uterine artery catheterization, a reversible gel foam was placed to control additional small vessel oozing from the surgical sites. The incision was closed with staples on post-operative day three, and she was discharged home on post-operative day six with a healthy baby and Hgb and PLT counts of 10.6 g/dL and $13 \times 10^9/\text{L}$, respectively.

COMMENT

This report outlines strategies for approaching the potentially conflicting priorities of the mother and fetus in the event of maternal haemorrhage, fetal distress and maternal labour for a woman with severe thrombocytopenia complicated by maternal alloimmunization. There are a number of strategies for managing alloimmune PLT refractoriness: (1) transfuse HLA-matched PLTs; (2) transfuse cross-matched PLTs, which

were tested with the patient's plasma; (3) transfuse ABO-compatible PLTs; and, if those options are not available, (4) repeated infusions of incompatible PLTs.^{9,10} Because HLA-matched PLTs are difficult to obtain, take several days to process and would have required multiple units from specially selected or matched donors to obtain the necessary volume, we chose to administer large amounts of single-donor PLTs to overwhelm the maternal immunological system. A case series of 119 pregnancies complicated by peripheral destruction/ITP reported moderate-severe bleeding in 21% ($n = 25$); 22% of the 18 women with PLT <50 lost >1 L of blood during delivery, but it is difficult generalize these data to our patient with a marrow production defect.¹¹ A letter reported a case of 'aplastic anaemia' with thrombocytopenia during pregnancy, but a bone marrow biopsy was not performed, and the PLT count increased after delivery.¹² The five-year survival rate for haematopoietic cell transplantation from an HLA-matched donor for aplastic anaemia is 56–89%, but this was not an option for our patient.⁴

The focus of this report is to demonstrate the importance of a multidisciplinary approach combining critical care medicine, obstetric medicine, haematology, interventional radiology and perinatology. The group met on a regular basis, wrote a critical care protocol for each possible scenario and their consequences, and prepared an advanced directive in case the patient became uncommunicative. This management plan proactively anticipated potential ethical and medical complications so that when interventions were required, the infrastructure was in place, and delays were avoided. It is our hope that the plan described will assist other clinicians in the future as we believe that this multidisciplinary collaborative approach minimized morbidity and decreased the risk of mortality in this challenging case.

Conflict of interest

The authors do not have any conflict of interest to declare regarding this manuscript.

Contributions to the manuscript

- (1) Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data: Dr Smolinsky, Dr Carson, Dr Guzman, Dr Ranzini, Ms Toscano, MT and Dr Bukhari;
- (2) Drafting the article or revising it critically for important intellectual content: Dr Smolinsky, Dr Carson and Dr Guzman;
- (3) Final approval of the version to be published: Dr Smolinsky, Dr Carson and Dr Guzman.

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