CASE REPORT

Neonatal alloimmune thrombocytopenia with significant HLA antibodies

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A case of neonatal alloimmune thrombocytopenia (NAIT) secondary to human platelet antigen (HPA)-1a antibodies is reported. Additional multispecific HLA antibodies rendered volunteer donor platelet transfusions ineffective. Despite a high incidence of maternal HLA antibodies in the pregnant population, there is only one previous report of clinically significant HLA antibodies.

Neonatal alloimmune thrombocytopenia (NAIT) results from human platelet antigen (HPA) incompatibility, with a reported incidence range of 1 in 1000 to 1 in 5000.^{1,2} Although HLA antibodies occur in up to one third of pregnancies, the fetus is usually protected. HLA antigens have only rarely been implicated as a cause of NAIT.³

We report a case of NAIT refractory to HPA matched volunteer donor platelet transfusions. Investigations confirmed the presence of antibodies to HPA-1a and strongly reactive multispecific antibodies to HLA class I. After infusion of maternal platelets, the platelet count rose.

We hypothesise that, although the HLA antibodies detected in our case did not cause the thrombocytopenia, they were active against volunteer donor platelets, rendering them ineffective. When HLA antibodies complicate NAIT, it is necessary to consider maternal platelet apheresis as a source of platelets while awaiting availability of platelets from HLA and HPA compatible volunteer donors. This may prevent neurological sequelae.

CASE REPORT

Twin 2 was the second of diamniotic twins delivered at term. Shortly after birth widespread petechial spots were noted. The platelet count was $5 \times 10^9/l$. The platelet count of the other twin was normal.

The mother was 37 years old, had no medical problems, and denied having any infections during pregnancy. A maternal blood count performed at 32 weeks gestation showed a platelet count of $306 \times 10^9/l$. The mother reported three previous pregnancies, with the first two resulting in spontaneous miscarriages at about seven weeks gestation. Her third pregnancy had been uneventful. The current pregnancy had also been uneventful apart from symmetrical in utero growth retardation. After delivery, placental histology showed a significant placental infarct.

A diagnosis of NAIT was made, and intravenous immunoglobulin was started. Infusion of 15 ml/kg HPA-1b volunteer donor platelets resulted in a poor platelet increment from 5×10^9 to $13 \times 10^9/l$. A cranial ultrasound scan showed an echodense region in the subarachnoid space, consistent with a subarachnoid haemorrhage. Further HPA-1b platelet transfusions continued to result in poor platelet increments. Prednisolone 1 mg/kg was started on day 2. An exchange transfusion was considered but not performed because of concern about the neurological status.

Table 1 Investigations

Platelet immunology	
Genotyping:	
Maternal platelet genotype:	HPA-1b1b; HPA-2a2a; HPA-3a3b; HPA-4a4a; HPA-5a5b
Paternal platelet genotype:	HPA-1a1b; HPA-2a2a; HPA-3a3a; HPA-4a4a; HPA-5a5a
Twin 1 platelet genotype:	HPA-1b1b; HPA-2a2a; HPA-3a3b; HPA-4a4a; HPA-5a5a
Twin 2 platelet genotype:	HPA-1a1b; HPA-2a2a; HPA-3a3a; HPA-4a4a; HPA-5a5b
Indirect platelet immunofluorescence (PIFT):	
IgG platelet antibodies detected in mother's serum	
Positive reactions with 6/6 HPA/HLA typed panel cells	
Monoclonal antibody specific immobilisation of platelet antigen assay (MAIPA):	
Anti-HPA 1a antibody detected, titre >1/16	
Solid phase ELISA (PAK):	
Anti-HPA 1a antibody detected, HLA antibodies also detected	
Crossmatch of maternal serum versus paternal platelets:	
Positive reactions between mother's serum and father's platelets	
Strongly positive for anti-GPIIb/IIIa	
HLA typing and antibody screen	
Class I typing:	
Mother:	A1; B8
Father:	A2; B27 B60
Twin 1:	A1 A2; B8 B60
Twin 2:	A1 A2; B8 B27
Lymphocyte cytotoxicity test (LCT):	
Maternal serum:	Multispecific HLA antibodies detected, titre >1/16
Infectious screen:	
Blood cultures:	Negative
Urine cultures:	Negative
TORCH:	Negative

Outcome

Investigations (table 1) confirmed the diagnosis of NAIT caused by HPA-1a antibodies with the additional finding of multispecific HLA class I antibodies. On day 3, 80 ml maternal platelet concentrate was collected using a Cobe Spectra cell separator. The platelets were irradiated but not washed, as this would have caused a clinically unacceptable delay. The concentrate was split into four 20 ml packs, each estimated to contain 25×10^9 platelets.

Despite receiving HPA matched platelets a few hours earlier, the platelet count immediately before the maternal platelet transfusion was only $12 \times 10^9/l$. The count rose to $101 \times 10^9/l$ after the first maternal platelet pack and subsequently to 206

Abbreviations: NAIT, neonatal alloimmune thrombocytopenia; HPA, human platelet antigen

Figure 1

$\times 10^9/l$ after infusion of a second within 24 hours. A repeat cranial ultrasound scan on the following day showed no evidence of an intracranial bleed.

Subsequent support for the neonate was maintained with donor HPA-1a negative platelets matched as closely as possible for the maternal HLA phenotype (fig 1).

The neonate was discharged home on day 20 with a stable platelet count and no evidence of neurological impairment.

DISCUSSION

HLA antibodies have been shown in 7–39% of pregnancies. Only HLA-A2 antibodies have been postulated to harm the fetus.⁴ The mechanisms by which the fetus is protected from these antibodies is not completely understood, with hypotheses including blocking antibodies and placental filtration.

The coexistence of HLA and HPA antibodies would be expected to occur in up to 1 in 2500 pregnancies. Despite this, we could only find a single report of HLA incompatibility causing platelet refractoriness in a case of NAIT.⁵ In this case, in utero transfusions of volunteer donor platelets had been given for a previously affected pregnancy, and it was hypothesised that these resulted in the development of HLA antibodies active against further in utero transfusions of volunteer donor platelets.

In this case, the mother had presumably developed HLA antibodies in response to earlier pregnancies. Although the maternal HLA antibodies were not thought to have contributed to the neonatal thrombocytopenia, it is postulated that they were expressed against HLA incompatible volunteer donor platelets, rendering them ineffective.

Two alternative explanations that cannot be excluded are firstly a late response to intravenous immunoglobulin and secondly absorption of the HLA antibodies as a result of the repeated initial transfusions with HLA incompatible donor platelets. Retrospectively, it would have been informative to have tested the serum of both twins for the presence and specificity of HLA antibodies. We are unable to comment on the significance of the placental infarct seen in this case.

Conclusion

In cases of NAIT, prompt correction of the thrombocytopenia is essential to minimise the risk of neurological complications. We report a case of NAIT in which HLA antibodies were postulated to cause platelet refractoriness. When faced with such a situation, in which finding cytomegalovirus negative donors matched for HPA and HLA can be difficult and slow, it is necessary to consider maternal platelet apheresis as a possible life saving source of safe platelets.

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REFERENCES

- Muller-Eckhardt C**, Kiefel V, Grubert A, *et al*. 348 cases of suspected neonatal alloimmune thrombocytopenia. *Lancet* 1989;1:363.
- Blanchette VS**, Chen L, Salomon de Friedberg Z, *et al*. Alloimmunisation to the P1^{AL} platelet antigen: results of a prospective study. *Br J Haematol* 1990;74:209.
- King SE**, Kao KJ, Bray PF, *et al*. The role of HLA antibodies in neonatal thrombocytopenia: a prospective study. *Tissue Antigens* 1996;47:206–11.
- Chow MP**, Sun KJ, Yung CH, *et al*. Neonatal alloimmune thrombocytopenia due to HLA-A2 antibody. *Acta Haematol* 1992;87:153–5.
- Murphy MF**, Metcalf P, Waters AH, *et al*. Antenatal management of severe fetal-maternal alloimmune thrombocytopenia: HLA incompatibility may affect platelet response to fetal platelet transfusions. *Blood* 1993;81:2174–9.