Post-Transfusion Purpura – When and Why?

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Alloimmunization against human platelet antigens may occur during pregnancy and following transfusion or transplantation as a consequence of the presence of foreign platelets in the circulation. The antibodies are directed against an antigen present on the foreign platelets, but absent from those of the host, due to polymorphisms of the major platelet membrane glycoproteins. Alloantibodies against HPA are responsible for clinical syndromes such as neonatal alloimmune thrombocytopenia, post-transfusion purpura, passive alloimmune thrombocytopenia, transplantation-associated alloimmune thrombocytopenia, and platelet transfusion refractoriness [1].

Single nucleotide polymorphisms in genes coding for platelet membrane glycoproteins account for almost all platelet-specific alloantigens [Table 1]. Most of them are located in the alpha and beta chains of the alpha-IIb/beta-3 (GPIIb/IIIa) integrin, the fibrinogen receptor. Other polymorphisms are located in the vWF receptor (GPIbα, GPIbβ), collagen receptor (GPIa, integrin α2) and CD109. The polymorphism HPA-1 (Leu33Pro in GPIIIa) is the one most frequently involved in PTP and neonatal alloimmune thrombocytopenia.

PTP is an extremely rare event characterized by acute episodes of severe immune thrombocytopenia occurring approximately a week after transfusion, observed exclusively in multiparous women or in polytransfused patients. In this issue of *IMAJ*, Shtalrid and co-authors [2] report their experience over 11 years during which they diagnosed six PTP patients, four women and two men, with a frequency of 1:24,000. As shown in this report, as well as other reports in the literature, PTP is strongly associated with alloimmunization against platelet-specific antigens. This phenomenon was originally described in HPA-1b/HPA-1b women who had been previously immunized by an HPA-1a-positive pregnancy. In such women, subsequent transfusion provokes a secondary (anamnestic) response, which boosts the patient's anti-HPA-1a antibody to extend its activity and to lose its specificity, which starts the destruction of the autologous HPA-1b (HPA-1a-negative) platelets. Later, it was shown that this phenomenon can also be caused by other antibodies such as HPA-1b, 2b, 3a, 3b, and 5b [3]. Moreover, HPA-15 alloimmunization was found in 3% of polytransfused patients, and in 1% without other platelet-reactive antibodies [4].

HPA = human platelet antigen
GP = glycoprotein
PTP = post-transfusion purpura

Table 1. Human platelet antigen (HPA) polymorphisms

Alloantigen	Platelet GP	CD	Nucleotide change	Protein isoforms	Gene frequency (Cauacasian)
HPA-1 a/b	GPIIIa (β3)	CD61	176 T>C	Leu33Pro	0.85/0.15
HPA-2 a/b	GPIbα	CD42b	482 C>T	Thr145Met	0.93/0.07
HPA-3 a/b	GPIIb (αIIb)	CD41	2621 T>G	Ile843Ser	0.61/0.39
HPA-4 a/b	GPIIIa (β3)	CD61	506 G>A	Arg143Gln	>0.99/<0.01
HPA-5 a/b	GPIa (α2)	CD49b	1600 G>A	Glu505Lys	0.89/0.11
HPA-6bw	GPIIIa (β3)	CD61	1544 G>A	Arg489Gln	>0.99/<0.01
HPA-7bw	GPIIIa (β3)	CD61	1297 C>G	Pro407Ala	>0.99/<0.01
HPA-8bw	GPIIIa (β3)	CD61	1984 C>T	Arg656Cys	>0.99/<0.01
HPA-9bw	GPIIb (αIIb)	CD41	2602 G>A	Val837Met	0.97/0.03
HPA-10bw	GPIIIa (β3)	CD61	263 G>A	Arg62Gln	>0.99/<0.01
HPA-11bw	GPIIIa (β3)	CD61	1976 G>A	Arg633His	>0.99/<0.01
HPA-12bw	GPIb β3	CD42c	119 G>A	Gly15Glu	
HPA-13bw	GPIa (α2)	CD49b	2483 C>T	Thr799Met	
HPA-14bw	GPIIIa (β3)	CD61	1909-11 delAAG	Lys611del	
HPA-15 a/b	GPI anchored protein	CD109	2108 C>A	Ser682Tyr	0.51/0.49
HPA-16bw	GPIIIa (β3)	CD61	497 C>T	Thr140Ile	

The alloantigen table includes published serologically defined platelet-specific antigens.

The pathophysiology of PTP is unclear. In many cases of HPA-1a-associated PTP, the antibodies were not restricted to HPA-1a epitope [5], some of them inhibited the adhesion to fibrinogen of both HPA-1a and HPA-1b-carrying cells [6], and in one case, the patient's acute-phase serum contained an additional antibody against GP120 protein expressed by Glanzmann thrombasthenia platelets but not by Bernard-Soulier platelets [7]. Taaning and Tonnesen [8] showed that during the thrombocytopenic phase, pan-specific antibodies against platelet GPIIb/IIIa, GPIb-IX and GPIa/IIa were formed, together with the HPA alloantibodies. These pan-reactive antibodies were probably responsible for the autologous destruction in PTP.

In their report [2], Shtalrid et al. describe three cases of PTP associated with HPA-3b, HPA-1b and HPA-3a respectively, the latter along with anti-HLA class-1 antibody. The authors suggest that PTP is more frequent than previously described, and may be misdiagnosed because of complications, as occurred in their patients (disseminated intravascular coagulation, infections,

autoimmune disorder, and heparin or penicillin therapy). PTP occurs in patients previously exposed to foreign platelets; it might be more common when the immunologic system is sensitized by the foreign platelets together with infections, drug-induced autoantibodies or an underlying autoimmune disorder. These complicated situations probably promote a transient development of pan-reactive antibodies responsible for the autologous platelet destruction in PTP.

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