REVIEWS

Platelet Antigens and Antiplatelet Antibodies

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Transfusion of allogenic platelets (TAP) is a potent therapeutic method for patients with impaired bone marrow platelet-producing function caused by endogenous depression of hemopoiesis or exogenous factors, such as radiation or cytostatic therapy. Transplantation of allogenic bone marrow from close relatives is impossible without TAP. Allogenic platelets are required for recipients in whom thrombopoiesis in the bone marrow ceases because of fractionated irradiation and cytostatic therapy, while transplanted cells do not yet function.

TAP is an expensive procedure. It costs at least $500 to attain a hemostatic effect by means of TAP in one patient. That is why it is particularly disappointing when platelet transfusion is ineffective because of immunological reasons which have been neglected by transfusiologist [1,2]. Immune conflict in TAP can be due to allosensitization caused by previous pregnancies and transfusion of blood components [2,10,11]. The conflict consists in rejection of donor platelets because of immune antibody production in the recipient. It considerably reduces the efficiency of therapy and even annihilate its therapeutic effect. The immune reaction can be associated with fever (nonhemolytic transfusion reaction) and the absence of increment in platelets count (refraction to platelet transfusion, RPT).

The main cause of immune complications in TAP are antibodies to HLA class I antigens expressed on T lymphocytes, polymorphonuclear leukocytes, and platelets [8,9]. It is believed that the more blood component transfusions (erythrocyte and platelet transfusions) are received by patients, the higher the incidence of antibody production and RPT [6]. Sensitizing doses for leukocytes and platelets are 15×10^8 and 18×10^{10}, respectively. The number of leukocytes in transfused blood components is the main factor causing the production of antiplatelet antibodies responsible for RPT. Leukocytes in a dose of 15×10^8 induced the production of anti-HLA antibodies in 25% recipients who had never had contacts with allogenic material. By contrast, leukocytes in a dose below 0.15×10^8 did not induce the production of anti-HLA antibodies and RPT. We can agree with some scientists considering that nylon filters separating erythrocytes from leukocytes notably reduce the number of recipients sensitized to platelets and apparently affects the formation of cell mediators [19].

Platelet count did not increase after allotransfusion in 84% patients with anti-HLA antibodies (Table 1), while in 16% recipients a notable increment was observed, mainly in cases when immunological tests, primarily the lymphocytotoxic test between donor cells and recipient serum were negative. By contrast, TAP increased platelet count in 65% recipients without anti-HLA antibodies and no platelet increment was observed in 35%, apparently because of their nonimmune consumption accompanying some pathological states, such as hemopoietic hypoplasia, sepsis, splenomegalia, disseminated intravascular coagulation, *etc.* [12]. In uncomplicated TAP, platelet count increases by 10,000-20,000 cells/μl. After 24 h it decreases by 10%. Transfusiologist should know exactly the increment in platelet count, recipient's temperature before and after TAP, and whether the recipient has antibodies reacting with platelets.

According to current views, TAP accompanied by nonhemolytical transfusion reaction or RPT with the formation of antiplatelet antibodies is immunologically incompatible with *a priori* unfavorable outcome.

Human platelet antigens (HPA) characteristic of platelets and not expressed on other blood cells are

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now intensely studied [15,17,22]. Some of them were detected on the endothelium and vascular smooth muscle cells, as well as on activated T lymphocytes [16]. These antigens constitute several diallele systems (Table 2). In particular, the HPA-1 system has HPA-1a and HPA-1b alleles. HPA-1a antigen frequently (95-99%) occurs in the population of Europe and Asia, while the incidence of HPA-1b is 26.0-26.8%. HPA-2 system includes abundant HPA-2a allele and rarely occurring HPA-2b allele (99 and 14.3%, respectively). Platelet antigen HPA-3 system is represented by HPA-3a and HPA-3b alleles occurring in 85-99 and 62-66% humans, respectively. Platelet antigens HPA-4a and HPA-4b are present in 1.65 and 99.9% patients, respectively. Little studied HPA-5, HPA-6, HPA-7, and HPA-8 antigen systems are also platelet-specific.

Patients with anti-HPA antibodies are more rare (no more than 5%) than with anti-HLA antibodies. The presence of anti-HPA is usually associated with anti-HLA antibodies. Identification of anti-HLA and anti-HPA antibodies is very important, because the presence of these antibodies largely determines the probability of immune reaction between patient serum and platelets and the possibility of choosing a compatible donor.

TABLE 1. Relationship between Increase in Platelet Count after Allotransfusion and the Presence of Anti-HLA Antibodies in Recipient

Anti-HLA antibodies	Increase in platelet count			
	no		yes	
	abs.	%	abs.	%
Yes	26	84	5	16
No	13	35	24	65

Anti-HLA antibodies are precisely detected in the lymphocytotoxic test. However this method cannot be used for detecting platelet antigens, because lympho-

TABLE 2. Human Allogenic Platelet Systems [21]

Platelet antigen names		Incidence of		Glycoproteins	Country (ethnic group)
old	new	genotype	phenotype		
PL^{A1} (Zw^a)	HPA-1a	0.8550	97.65		Netherlands
0.8300	97.00				USA
0.8500	97.75				Germany
0.9360	99.60			IIIa	USA (Blacks)
0.9900	99.90				Japan
PL^{A2} (Zw^b)	HPA-1b	0.1550	26.80		Netherlands
0.1700	26.00				USA
0.9900					Japan
$Ko^{a(Siba)}$	HPA-2b	0.0740	14.30	Ib	Netherlands
Ko^b	HPA-2a	0.9230	99.40		Netherlands
Bak^a	HPA-3a	0.6960	90.76	IIb	USA
0.6100	85.00				Japan
0.5410	78.90				
Bak^b	HPA-3b	0.3900	66.00		USA
0.3650	62.62				Germany
Yuk^b (Pen^a)	HPA-4b	0.9917	99.90	IIIa	Japan
Yuk^a (Pen^b)	HPA-4a	0.0083	1.65		Japan
Br^a (Zav^a)	HPA-5b			Ia	
Br^b (Zav^b)	HPA-5b				
Ca^b Tu	HPA-6a			IIIa	
Ca^a Tu	HPA-6b				
Mo^b	HPA-7a			IIIa	
Mo^a	HPA-7b				
Sr^b	HPA-8a			IIIa	
Sr^b	HPA-8b				

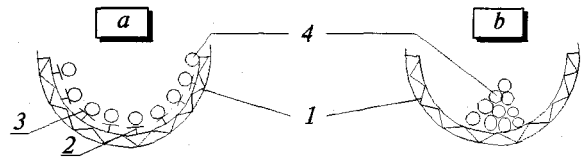

Fig. 1. Positive (*a*) and negative (*b*) tests for anti-HLA and anti-HPA antibodies. Solid-phase hemagglutination on platelet monolayer (method [17] with our modifications): *1*) platelet monolayer; *2*) anti-HLA and anti-HPA antibodies; *3*) antiglobulin serum antibodies; *4*) indicator platelets.

cytes express no HPA antigens. Enzyme immunoassay is a universal method for detecting anti-HLA and anti-HPA antibodies reacting with platelets [1]. A promising method of platelet modification is 1-h exposure of platelets in isotonic medium at pH 3-4. This procedure destroys glycoprotein determinants of HLA, but not HPA [14,20,21]. Comparison of enzyme immunoassay with native and modified platelets easily and accurately identifies the presence of anti-HLA, anti-HPA, or both antibodies in the serum.

Express test for compatibility between patient serum and donor platelets opens new vistas in individual selection of immunologically compatible platelets (Fig. 1). The use solid-phase hemagglutination on a platelet monolayer allows to exclude donors incompatible by platelet antigen because of recipient's anti-HLA and anti-HPA antibodies [18] and thus avoid *a priori* ineffective TAP accompanied by nonhemolytical transfusion reactions and RPT. Moreover, HPA can cause autosensitization, thrombocytopenia, and immune thrombocytopenic purpura [23]. Autoimmune anti-HPA antibodies are usually represented by IgG (92%), are rarely IgM and IgA (42 and 6%, respectively).

It is noteworthy that the production of antiplatelet autoantibodies can be associated with the presence of antiphospholipid antibodies and the development of characteristic disorders: recurrent thrombosis of main vessels, cardiac and brain vessels, fetal vessels during pregnancy eventuating in stillbirth and other abnormalities [3,5]. This can explain stable association of antiphospholipid antibodies with autoimmune hemolytic anemia and direct Coombs' test and lymphoproliferative disease complicated by immune thrombocytopenia [4,13]. The presence of platelet antigens and antiplatelet antibodies seems to be an important factor determining both maintenance of homeostasis and the development of pathology.

REFERENCES

1. E. M. Anfimova, S. G. Khaspekova, I. V. Vlasova, and A. V. Mazurov, *Byull. Eksp. Biol. Med.*, **125,** No. 5, 596-600 (1998).
2. E. A. Zotikov, *Human Antigenic Systems and Homeostasis* [in Russian], Moscow (1982).
3. E. L. Nasonov, *Klin. Med.*, No. 1, 5-13 (1989).
4. E. L. Nasonov, Z. S. Alekberova, L. Z. Prudnikova, *et al.*, *Ibid.*, No. 11, 100-106 (1987).
5. E. L. Nasonov, Z. S. Alekberova, and K. V. Solozhin, *Ter. Arkh.*, No. 6, 46-49 (1996).
6. L. P. Poreshina, A. M. Komponeets, R. M. Kut'ina, *et al.*, *Immunologiya*, No. 4, 26-29 (1993).
7. T. M. Reshetnyak, Z. S. Alekberova, E. L. Nasonov, and V. A. Nasonova, *Ter. Arkh.*, No. 5, 83-86 (1998).
8. J. Dausset, M. Colin, and J. Colombani, *Vox Sang.*, **5,** 4 (1960).
9. J. P. Dutcher, C. A. Schiffer, J. Aisner, and P. H. Wiernik, *Blood*, **57,** No. 3, 395-398 (1981).
10. D. F. Friedman, M. B. Lukas, A. Jawad, *et al.*, *Ibid.*, **88,** No. 8, 3216-3222 (1996).
11. L. A. Harker, L. Roskos, and E. Cheung, *Transfusion*, **38,** No. 7, 619-621 (1998).
12. E. N. Harris, A. E. Gharavi, S. Loizou, *et al.*, *J. Clin. Lab. Immunol.*, **16,** No. 1, 14-17 (1985).
13. K. J. Kao, *Transfusion*, **28,** No. 1, 14-17 (1998).
14. T. S. Kickler, H. Braine, and P. M. Ness, *Ibid.*, **25,** No. 4, 385-389 (1985).
15. O. C. Leeksma, J. C. Giltay, J. Zandbergen-Spaargaren, *et al.*, *Br. J. Haematol.*, **66,** No. 3, 369-373 (1987).
16. C. Muller-Eckhardt, K. Kiefel, and S. Santos, *Transf. Med.*, **4,** 98-109 (1990).
17. J. M. Rachel, L. T. Sinor, O. W. Tawfick, *et al.*, *Med. Lab. Sci.*, **42,** No. 2, 194-195 (1985).
18. C. B. Sarkodee-Adoo, J. M. Kendall, R. Sridhara, *et al.*, *Transfusion*, **38,** No. 3, 229-235 (1998).
19. A. Shanwell, S. Sallander, I. Olsson, *et al.*, *Br. J. Haematol.*, **79,** No. 3, 462-465 (1991).
20. S. Sugawara, T. Abo, and K. Kumagai, *J. Immunol. Methods*, **100,** No. 1-2, 83-90 (1987).
21. M. J. Telen and N. Rao, *Curr. Opin. Hemat.*, **1,** Mo. 2, 143-150 (1994).
22. A. H. Waters, *Practical Haematology*, eds. J. V. Dacie and S. M. Lewis, 8th ed., New York (1995), pp. 465-476.