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The presence of anti-D antibodies after kidney and liver transplantation in cases of ABO identical donor-recipient pairs

Obecność przeciwciał anty-D po przeszczepieniu nerki i wątroby w parach dawca-biorca identycznych pod względem ABO

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Słowa kluczowe

transplantacja narządu, mała niezgodność grup krwi, niezgodność dawca-biorca

Summary

Introduction. Donor-derived antibodies against RBCs antigens can be sometimes detected in recipients of solid organs. Usually they are anti-A or anti-B, rarely they have other specificity.

Aim. Assessment of antibodies in recipients of kidney and liver derived from immunised female donors despite of postpartum immunoprophylaxis.

Material and methods. Blood samples from two recipients after kidney and two after liver transplantation. The routine type and screen and direct antiglobulin test with recipients' RBCs by the microcolumn gel method. The antibody acid elution and indirect antiglobulin test for detection of antibodies in each eluate and serum from the recipients. Identification of antibodies by the IAT and panel RBCs.

Results. Four patients were RhD positive and identical in ABO in each pair donor-recipient. Three female donors were RhD negative. In all recipients anti-D antibodies were strongly reactive, detected on RBCs by the DAT and in the serum and eluate by the IAT, regardless of their reactivity in the donor serum. Individual recipients received: 2, 5, 8 and 14 units of RhD negative RBCs and they needed transfusion during the time from one day to 7 weeks.

Conclusions. Despite of obligatory anti-D immunoprophylaxis used in RhD negative women, they can be immunized ante- or postpartum and their lymphocytes transferred with transplanted organs can produce anti-D in RhD positive recipients. Serological tests for antibody detection and identification in these patients during first two weeks after transplantation can be useful in predicting immune haemolytic anaemia.

Streszczenie

Wstęp. Po transplantacji narządów czasem u biorcy można wykryć przeciwciała pochodzące od dawcy i skierowane przeciw krwinkom czerwonym. Zazwyczaj są to anty-A lub anty-B, rzadko mają inną swoistość.

Cel pracy. Ocena przeciwciał u biorców nerki i wątroby pochodzących od dawczyń zimmunizowanych mimo stosowanej immunoprofilaktyki poporodowej.

Materiał i metody. Próbki krwi dwóch biorców po transplantacji nerki i dwóch po transplantacji wątroby. Rutynowe oznaczenie grupy krwi i bezpośredni test antyglobulinowy z krwinkami biorców wykonany techniką mikrolumnową z żelem. Kwaśna elucja przeciwciał i pośredni test antyglobulinowy w celu wykrycia przeciwciał w eluacie oraz w surowicy biorców. Identyfikacja przeciwciał za pomocą PTA i zestawu krwinek wzorcowych.

Wyniki. Wykryto allo-anty-D u dwóch biorców po przeszczepieniu nerki i u dwóch po przeszczepieniu wątroby. Czterech pacjentów było RhD dodatnich oraz byli identyczni z dawcami w zakresie ABO w każdej z par. Dawcami były trzy RhD ujemne kobiety. U wszystkich biorców przeciwciała anty-D były wyraźnie aktywne, wykrywalne na krwinkach w BTA oraz w surowicy i eluacie w PTA, niezależnie od ich reaktywności w surowicy dawcy. Poszczególni biorcy otrzymali: 2, 5, 8 i 14 jednostek krwinek czerwonych i potrzebowali przetoczeń od jednego dnia do 7 tygodni.

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Wnioski. Pomimo stosowania immunoprofilaktyki anty-D u RhD ujemnych kobiet, mogą one zostać uodpornione podczas ciąży i porodu, a ich limfocyty przeniesione z przeszczepianym narządem mogą wytwarzać przeciwciała anty-D u RhD dodatnich biorców. Badania serologiczne w celu wykrycia i identyfikacji przeciwciał u tych pacjentów w ciągu dwóch tygodni po transplantacji mogą być pomocne w przewidywaniu niedokrwistości immunohemolitycznej.

INTRODUCTION

Post-transplant haemolytic reactions due to red blood cell (RBC) alloantibodies have been observed in the recipients of haematopoietic stem cells (HSCs) because half of all donor-recipient pairs are ABO blood group mismatched (1). In so-called minor blood group incompatibility (donor antibodies against recipient antigens) antibodies anti-A, anti-B or others, e.g. anti-D, anti-E, anti-K etc. are produced by passenger lymphocytes accompanying HSCs from O or D negative, E-negative, K-negative etc. donors (2, 3). Organ transplants should be the same (e.g. recipient A, donor A), but also may be compatible in ABO (recipient A, B or AB, donor O). It causes a possibility of minor blood group incompatibility with symptoms similar to that after HSC transplantation (HSCT) (4-8). RBC antibody production after organ transplantation depends on the lymphoid mass transplanted. The frequency of antibody presence were lowest after kidney, intermediate after liver and highest after lung transplantation (9). Donor-derived antibodies are usually anti-A or anti-B but sometimes they can appear in the recipient identical in ABO blood group with the donor. Antibodies of different specificity than ABO can develop from lymphocytes transferred with the organ from immunized donors but this phenomenon is rarely observed (5, 7).

AIM

The aim of our study was to assess antibodies in recipients of kidney and liver, derived from female donors immunised despite of postpartum immunoprophylaxis.

MATERIAL AND METHODS

Samples of patient's whole blood were drawn, one in EDTA and one in a pure tube. ABO and Rh blood group typing were performed with the standard tube agglutination method using commercially available specific monoclonal antibodies and RBCs. The direct antiglobulin test (DAT) for antibody detection on RBCs and indirect antiglobulin test (IAT) for detection and identification of free antibodies in the serum and eluate were performed using gel agglutination tests (DiaMed ID, Switzerland). Commercial panels of RBCs for IAT were used (DiaMed, Switzerland and Diagnostic Grifols, España). Eluates from RBCs were prepared by routine acid elution technique with glycine/EDTA buffer pH 1.5. The titre of anti-D in two patients was determined by testing serial twofold dilutions of the serum and eluate with selected RhD positive heterozygous RBCs (DCcee). In the next two patients strength of agglutination was assessed in undiluted sera and eluates.

RESULTS

Kidney transplants

Forty three year-old male and 57 year-old female recipients with the same blood group AB RhD+ CCee K- received the kidney from the female donor with blood group AB RhD-. She had allo-anti-D active in the enzyme test and non-active in the IAT. In the 18th day after transplantation the recipients needed RBC transfusion because of anaemia and haemolysis. Table 1 shows serological results of both of them.

Liver transplants

Fifty seven year-old female recipient with blood group O RhD+ CcEe K- received the liver from the female donor O RhD-. In the 14th day after transplantation the patient needed RBC transfusion because of anaemia and haemolysis. She received 5 units of RBCs during 2 weeks.

Sixty four year-old male recipient with blood group O RhD+ Ccee K- received the liver from female donor O RhD-. In the 21st day after transplantation he needed RBC transfusion because of anaemia and haemolysis and once received 2 units of RBCs. Table 2 shows serological results of both patients.

Table 1. Serological results and RBC transfusions in two patients after kidney transplantation

Patient	DAT					Antibody specificity	Anti-D titre by IAT		No. of RBC units transfused
	IgG	IgA	IgM	C3c	C3d		serum	eluate	
1	4+	1+	0	0	0	anti-D	8	64	8 during 4 weeks
2	4+	0	0	0	0	anti-D	4	64	14 during 7 weeks

Table 2. Serological results and RBC transfusions in two patients after liver transplantation

Patient	DAT		Antibody specificity	Anti-D by IAT		No. of RBC units transfused
	IgG	C3d		serum	eluate	
1	4+	0	anti-D	2+	3+	5 during 2 weeks
2	4+	0	anti-D	2.5+	3+	2 in one day

DISCUSSION

According to literature the risk of antibody presence and haemolysis is lowest in kidney transplants, 17% and 9% respectively, followed by liver, 40% and 29% (9). It mainly refers to the formation of antibodies within ABO system after transplantation of grafts from O donors to A, B, AB blood group recipients. Rh factor is usually not considered significant in matching organ for transplantation (6). Approximately 10% of ABO-compatible transplants involve a D- donors and D+ recipients (7). Only few authors have been describing anti-D antibodies and haemolysis in such cases (10-12). This happened when the donor was a woman and she was previously pregnant. Analysis of over 34,000 transplants reported that grafts from female donors transplanted into male recipients have a 20% increased risk of graft loss as compared to gender matched male recipients (5). Other authors have reported no such difference in graft loss rates (7). We think that poor prognosis may depend on other factors than RBCs antibodies, e.g. antibodies against male-specific minor histocompatibility antigens HY which are present in 30% of women and can be responsible for the negative effect of transfusions from female blood donors to male recipients (13).

Alloantibodies to RBCs and haemolysis may be one of the risk factors in minor incompatibility after HSCT and solid organ transplantation. RBCs transfusion is appropriate therapy in such cases. The following question is important: how long donor lymphocytes transferred in grafts can produce RBCs antibodies? Some authors reported that ABO antibodies are absent three months after HSCT transplantation, whereas anti-D persisted for up to 1 year, subpopulation of B cells, which could produce antibodies were found in the circulation of transfusion recipients up to 1.5 years and mixed chimerism between donor cells and recipient kidney and blood cells was found up to 23 years (4). Despite these, post-transplant immune haemolysis is generally short-lived because the lymphocytes transferred with the donor organ are able to proliferate only temporarily, and antibody production gradually decreases as the passenger lymphocytes reach the end of their life span. For instance the antibodies persist for a median of 5 weeks in kidney transplant recipients, they were detected from 1st to 19th day after transplantation and patients required 4 to 14 RhD negative RBC units. Our recipients of kidney and liver had allo-anti-D causing haemolysis which occured between 2nd and 3rd week after transplantation and required from 2 to 14 RhD negative RBC units. In few described cases corticosteroid therapy and splenectomy were needed (7).

There is a main difference between minor incompatibility after HSCT and organ transplantation. In the first situation, RBCs after a few weeks are of the donor origin and then they do not have specific antigens for donor alloantibodies. After organ transplantation alloantibodies are produced by donor lymphocytes but RBCs by recipient bone morrow.

CONCLUSIONS

Despite of anti-D obligatory immunoprophylaxis used in RhD negative women, they can be immunized ante- and postpartum and their lymphocytes transferred with transplanted organs can produced anti-D in RhD positive recipients. Serological tests for antibody detection and identification in these patients during first two weeks after transplantation can be useful in predicting haemolytic anaemia.

BIBLIOGRAPHY

1. Booth GS, Gehrie EA, Savani BN: Minor RBC Ab and allo-SCT. Bone Marrow Transplant 2014; 49: 456-457.
2. Holbro A, Stern M, Infanti L et al.: Impact of recipient ABH secretor status on outcome in minor ABO-incompatible hematopoietic stem cell transplantation. Transfusion 2015; 55: 64-69.
3. Watz E, Remberger M, Ringden O et al.: Analysis or donor ABO incompatibility and antibody-associated complications after allogenic stem cell transplantation with reduced-intensity conditioning. Biol Blood Marrow Transplant 2014; 20: 264-271.
4. Opelz G, Morath Ch, Susal C et al.: Three-year outcomes following 1420 ABO-incompatible living-donor kidney transplants performed after ABO antibody reduction: results from 101 centers. Transplantation 2015; 99: 400-404.
5. Hareuweni M, Merchav H, Austerlitz N et al.: Donor anti-Jk^a causing hemolysis in a liver transplant recipient. Transfusion 2002; 42: 363-367.
6. Srinivas Reddy M, Varghese J, Venkataraman J, Rela M: Matching donor to recipient in liver transplantation: Relevance in clinical practice. World J Hepatol 2013; 5: 603-611.
7. Fung MK, Sheikh H, Eghtesad B et al.: Severe hemolysis from D incompatibility in a case of ABO-identical liver transplant. Transfusion 2004; 44: 1635-1639.
8. Dubey A, Pandey H, Sonker A et al.: A case of passenger lymphocyte syndrome following minor ABO incompatible renal transplantation. Asian J Transfus Sci 2014; 8: 56-58.
9. Hows J, Beddow K, Gordon-Smith C et al.: Donor-derived red blood cell antibodies and immune hemolysis after allogenic bone marrow transplantation. Blood 1986; 67: 177-181.
10. Schwartz D, Gotzinger P: Immune haemolytic anaemia (IHA) after solid organ transplantation due to Rhesus antibodies of donor origin: report of 5 cases. Beitrage Zur Infusiontherapie 1992; 30: 367-369.
11. Lee J-H, Mintz PD: Graft versus host anti-Rho (D) following minor Rh-incompatible orthotopic liver transplantation. Am J Hematol 1993; 44: 168-171.
12. Seltsam A, Hell A, Heymann G et al.: Donor-derived alloantibodies and passenger lymphocyte syndrome in two of four patients who received different organs from the same donor. Transfusion 2001; 41: 365-370.
13. Middelburg RA, Briet E, van der Bom JG: Mortality after transfusions, relation to donor sex. Vox Sang 2011; 101: 221-229.

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