Original Article

Title: Incidence and Pattern of Hemolytic Anemia After Minor ABO-mismatched Living-donor Lobar Lung Transplantation

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A Brief Title: Hemolysis after minor ABO-mismatched living-donor lung transplantation

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Keywords: ABO-mismatch, hemolytic anemia, living-donor lobar lung transplantation

Footnotes

Presented, in part, at the 47th Annual Congress of the Japan Society for Transplantation, October 4–7, 2011, Sendai, Japan.

Abstract

Living-donor lobar lung transplantation (LDLLT) has been successfully performed in Japan. In LDLLT, the recipient usually receives each lower lobe from 2 donors; however, finding two ABO-matched donors is often difficult. Solid organ transplantation from donors with minor ABO-mismatches can be complicated by hemolysis. We investigated the incidence of *de novo* anti-ABO antibody production and hemolysis in patients receiving LDLLT across minor ABO-mismatches. We evaluated 23 patients who underwent LDLLTs between June 2008 and December 2011, including 11 patients received minor ABO-mismatched transplantations. We measured the anti-A/B antibodies serum titers, hemoglobin concentrations, and indirect bilirubin levels. None of the patients showed any clinical sign of hemolytic anemia (mean follow-up period, 16 months). Two of the 11 patients (18%) receiving minor ABO-mismatched LDLLTs showed a small amount of *de novo* anti-B antibody for a transient period. These patients showed gradual progression of anemia, and weak *de novo* anti-A/B antibodies were detected by column agglutination technology. They received only 2 units of washed type O red blood cells; thereafter, hemolytic anemia did not develop further. In conclusion, LDLLT across minor ABO-mismatches made a transient appearance of weak *de novo* anti-A/B antibodies with low incidence, thus, it could be a safe treatment.

Introduction

The shortage of organ donors for patients requiring lung transplantation is more critical than that for any other solid organ. To address this issue, living-donor lobar lung transplantation (LDLLT) has been performed in Japan since 1998 [1,2]. After the Japanese organ transplantation law was revised, the frequency of lung transplantations from brain-dead donors increased, but the necessity of LDLLT particularly in the case of urgent patients remains unchanged. According to the current protocol for LDLLT, performing LDLLT from 2 ABO-matched donors is often difficult. Solid organ transplantation from donors with minor ABO-mismatches can be complicated by hemolysis [3,4], whereas we cannot help conducting LDLLT from minor ABO-mismatched donors. We reviewed our single-institutional experience of LDLLT and investigated the incidence of *de novo* anti-ABO antibody production and hemolysis in patients receiving LDLLT across minor ABO-mismatches.

Patients and Methods

We performed LDLLTs at Kyoto University for 25 patients between June 2008 and December 2011. Two patients were excluded because 1 patient died of multiple organ failure unrelated to ABO-mismatches in the early phase of the post-transplant period, and 1 received major ABO-mismatched transplantation. The case of a patient with major ABO-mismatched transplantation has been reported previously; the patient had O+ erythrocytes without anti-A/B antibody after bone marrow transplantation and received lobar lung transplants from donors with B+ and AB+ blood groups [5]. Therefore, we assessed 11 minor ABO-mismatched and 12 ABO-identical recipients. We measured the serum titers of anti-A and anti-B antibodies, determined rhesus phenotypes, and screened for irregular antibody, using column agglutination technology (CAT), for all patients, post-transplant day (PTD) 5, 8, and 14 routinely. When hemolytic anemia related to anti-A or anti-B

antibodies was suspected, their serum titers were measured. Moreover, if blood transfusion was necessary, cross-matching was performed using standard tube methods and/or CAT. We used hemoglobin concentration and indirect bilirubin levels to determine hemolysis. Each patient had been given an adequate explanation about the nature of the proposed investigation or treatment, and informed consent had been obtained.

Results

Among the 11 patients who received minor ABO-mismatched transplantation, 3 pediatric patients underwent transplantation of a single lobe. The remaining 8 adult patients underwent transplantation of both lung lobes: 3 from both donors with minor ABO-mismatch (Table 1). One patient died of pneumonia at 3 months after transplantation, and the others were alive; none of the patients showed any clinical sign of hemolytic anemia (follow-up period 3.3–44.7 months; mean, 16 months). Two of the 11 patients (18%) who received minor ABO-mismatched transplantation showed small amounts of *de novo* anti-A/B antibodies on PTD 27 and 39. The remaining 12 patients who received ABO-identical transplantation in the same period did not show the presence of *de novo* anti-A/B antibody.

Case 1

A 28-year-old woman, blood group B+, with idiopathic interstitial pneumonia underwent LDLLT with a right lower lobe from her mother (58 years; blood group, O+) and a left lower lobe from her aunt (56 years; blood group, O+). She received 34 units of type B red blood cells during the intraoperative period. The postoperative course was relatively uneventful. Immunosuppressive therapy included 3 drugs, namely, cyclosporine, azathioprine, and prednisone. The first episode of acute rejection on PTD 5 required intravenous administration of high-dose methylprednisolone and alteration of azathioprine to mycophenolate mofetil; the

second episode of acute rejection on PTD 10 required the same steroid therapy as that administered on PTD 5 and cyclosporine was changed to tacrolimus. On PTD 12, she received 2 units of type B red blood cells because of a progressive decrease in hemoglobin concentrations. Anemia gradually progressed again from PTD 21, and weak anti-B antibodies were detected by CAT and confirmed by standard tube methods on PTD 27. Levels of indirect bilirubin increased during this period. She received 2 units of red cell concentrates since PTD 7 until the appearance of anti-B antibodies. Subsequently, she has received only 2 units of washed type O red blood cells, and further progression of hemolytic anemia has not been observed (Fig. 1).

Case 2

A 44-year-old man, blood group O+, had acute myeloid leukemia and received allogeneic peripheral blood stem cell transplantation (PBSCT) from his sister (blood group, B+) 7 years back. Thereafter, his blood group became B+. About a year after PBSCT, he developed bronchiolitis obliterans syndrome (BOS), and his respiratory function gradually deteriorated. Seven years after PBSCT, he underwent LDLLT with a right lower lobe from his brother (50 years; blood group, O+) and a left lower lobe from his wife (54 years; blood group, B+). Because of severe pleural adhesions, he received 92 units of type B red blood cells during the intraoperative period. Immunosuppressive therapy consisted of 3 drugs, including cyclosporine, mycophenolate mofetil, and prednisone. The patient received 4 and 2 units of type B red blood cells on PTDs 4 and 8, respectively, because of a decrease in hemoglobin concentrations. On PTD 14, intrathoracic hematoma was removed with 8 units of type B red blood cells. In planning blood transfusion for progressive anemia on PTD 39, anti-B antibodies were not detected by CAT and standard tube methods. Cross-matching with type B red blood cells was performed using CAT because that day was a holiday, and the results revealed a positive cross-match. Levels of indirect bilirubin were high during this period. The patient received

8 units of red cell concentrates since PTD 7 until the appearance of anti-B antibodies. Subsequently, he has received only 2 units of washed type O red blood cells, and further progression of hemolytic anemia has not been observed (Fig. 2).

Discussion

Production of ABO antibodies by the graft against the recipient's red blood cells has previously been reported after transplantation of minor ABO-mismatched solid organs [3]. The passenger lymphocyte syndrome (PLS) is the clinical phenomenon of autoimmune hemolysis resulting from the adoptive transfer of viable lymphocytes from the donor during solid organ or hematopoietic stem cell transplant, and the frequency of PLS appears to be related to the volume of transplanted lymphoid tissue [6,7]. Typically, antibodies appear 7 to 10 days after transplantation, and are present for about 1 month. Several authors have found that the immunoglobulins primarily belong to the IgG class [8]. Ramsey et al. reported that the incidence of antibody detection and hemolysis was infrequent in kidney transplant patients, intermediate in liver transplant patients, and the highest in heart-lung transplant patients [3]. Magrin et al. reported hemolytic anemia across minor ABO-mismatch in a lung-only transplant recipient for the first time [9]; since then, several reports have been published to date [4,10-12]. Taaning et al. reported the case of patient with severe hemolysis caused by graft-derived anti-B production after bilateral lung (O group to B group) transplantation [10]. Salerno et al. reported 4 single and 3 bilateral lung transplant patients with minor ABO-mismatched transplants. Two of the 4 patients who received single lung transplants developed donor ABO antibody-derived hemolysis [4]. Sano et al. reported the cases of 13 patients with minor ABO-mismatched LDLLT of whom 5 developed anti-A or B antibody in the serum but only 1 showed hemolytic anemia [11,12]. In our study, we evaluated 11 patients with minor ABO-mismatched LDLLT of whom 2 developed anti-B antibodies in the serum and both of them

showed hemolytic anemia. A LDLLT recipient requires 2 ABO-identical or minor ABO-mismatched donors; therefore, the tendency of minor ABO-mismatches is high in LDLLT. In our study, 3 of the 8 adult patients who underwent LDLLT had both grafts across minor ABO-mismatches (Table 1). However, the incidence of hemolytic anemia in our study was low and recovered immediately.

About 20 years ago, CAT was introduced to automate immunohematology testing [13]. At our institution, we routinely use CAT first for the several following reasons. The sensitivity of CAT is better than that of standard tube methods. In addition, IgG class of anti-A/B antibodies is clinically more important than the IgM class; therefore, CAT, which detects antibodies belonging to IgG class more easily than standard tube methods, is more reasonable. Historically, testing before blood transfusion to determine the ABO group and D type has been performed by visually scoring antibody-mediated RBC agglutination in test tubes after centrifugation [14]. In Case 2 of this study, alloantibody was not detected by CAT and standard tube testing, but a few alloantibodies were detected by CAT during cross-matching.

In the event of a hemolytic crisis due to donor ABO antibodies, washed type O red blood cells were administered at our institution. Ogo et al. [15] and Bakr et al. [16] also reported the use of washed type O red blood cells against hemolytic anemia in living-donor lobar lung and kidney transplantations. By contrast, Hunt et al. reported the successful use of group O red blood cells [8]. Petz described that although packed red blood cells will contain anti-A and/or anti-B that are reactive with the patient's red blood cells, hemolysis caused by transfusion of plasma in red blood cells is rare so that using washed red blood cells is generally unnecessary [17]. To minimize a possible adverse effect of transfusion, we used washed type O red blood cells. Our option might lead to the smooth recovery from hemolytic anemia. In conclusion, LDLLT across minor ABO-mismatches made a transient appearance of weak *de novo* anti-A/B antibodies with low incidence. Despite of small number of cases, LDLLT could be a safe treatment.

Conflict of interest

Akihiro Ohsumi and co-authors have no conflict of interest.

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Legends

Table 1

Characteristics of blood type and number of cases of donors and recipients.

Figure 1

Trend of hemoglobin concentration and indirect bilirubin, and presence of anti-B antibody in Case 1.

Figure 2

Trend of hemoglobin concentration and indirect bilirubin, and presence of anti-B antibody in Case 2. -*: negative in anti-B antibody, but positive in cross-matching with type B red blood cells

Fig. 1

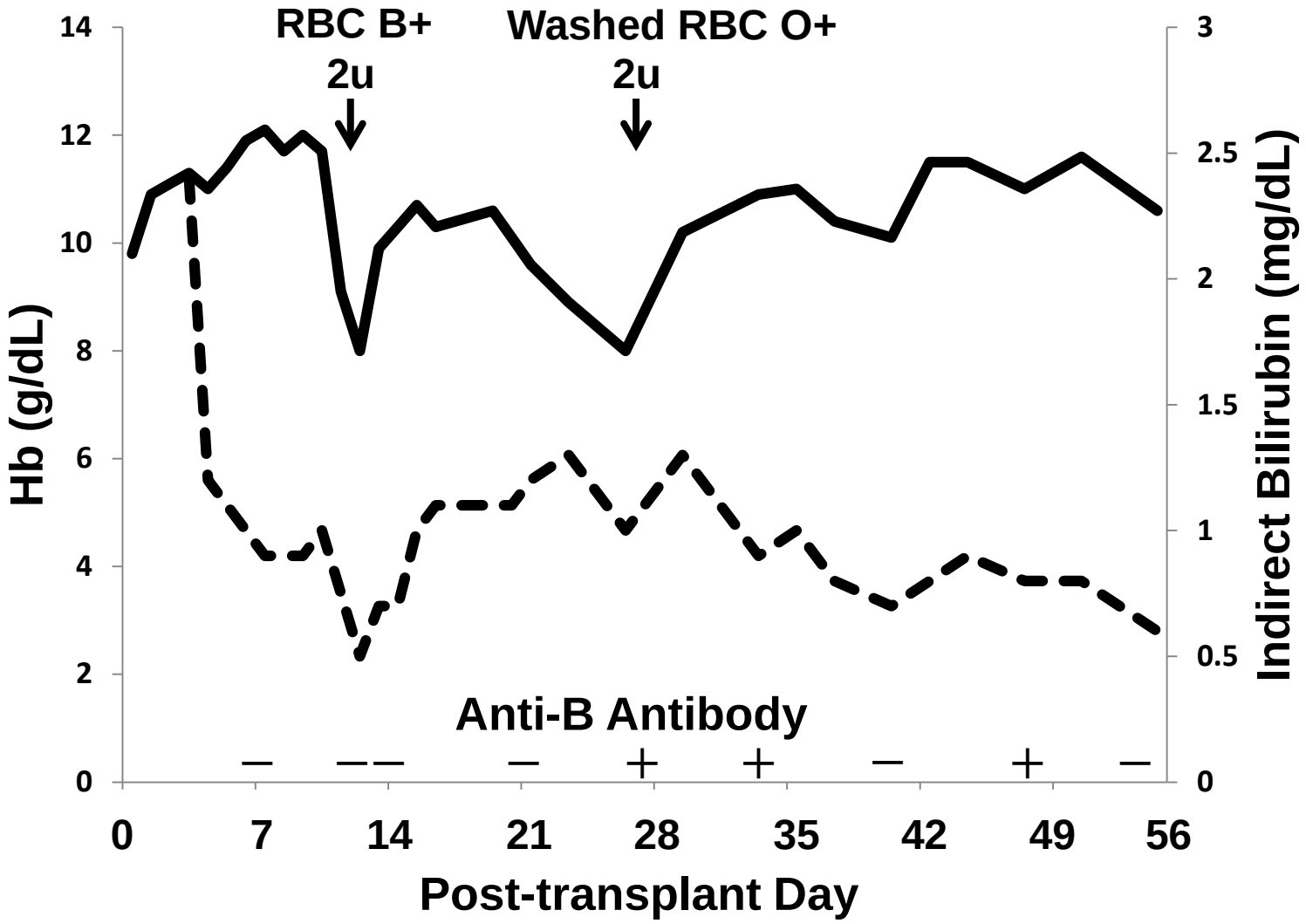
RBC B+
2u
Washed RBC O+
2u
Hb (g/dL)
Indirect Bilirubin (mg/dL)
Anti-B Antibody
– – – – + + – + –
Post-transplant Day
0
7
14
21
28
35
42
49
56
14
12
10
8
6
4
2
0
3
2.5
2
1.5
1
0.5
0

Fig. 2

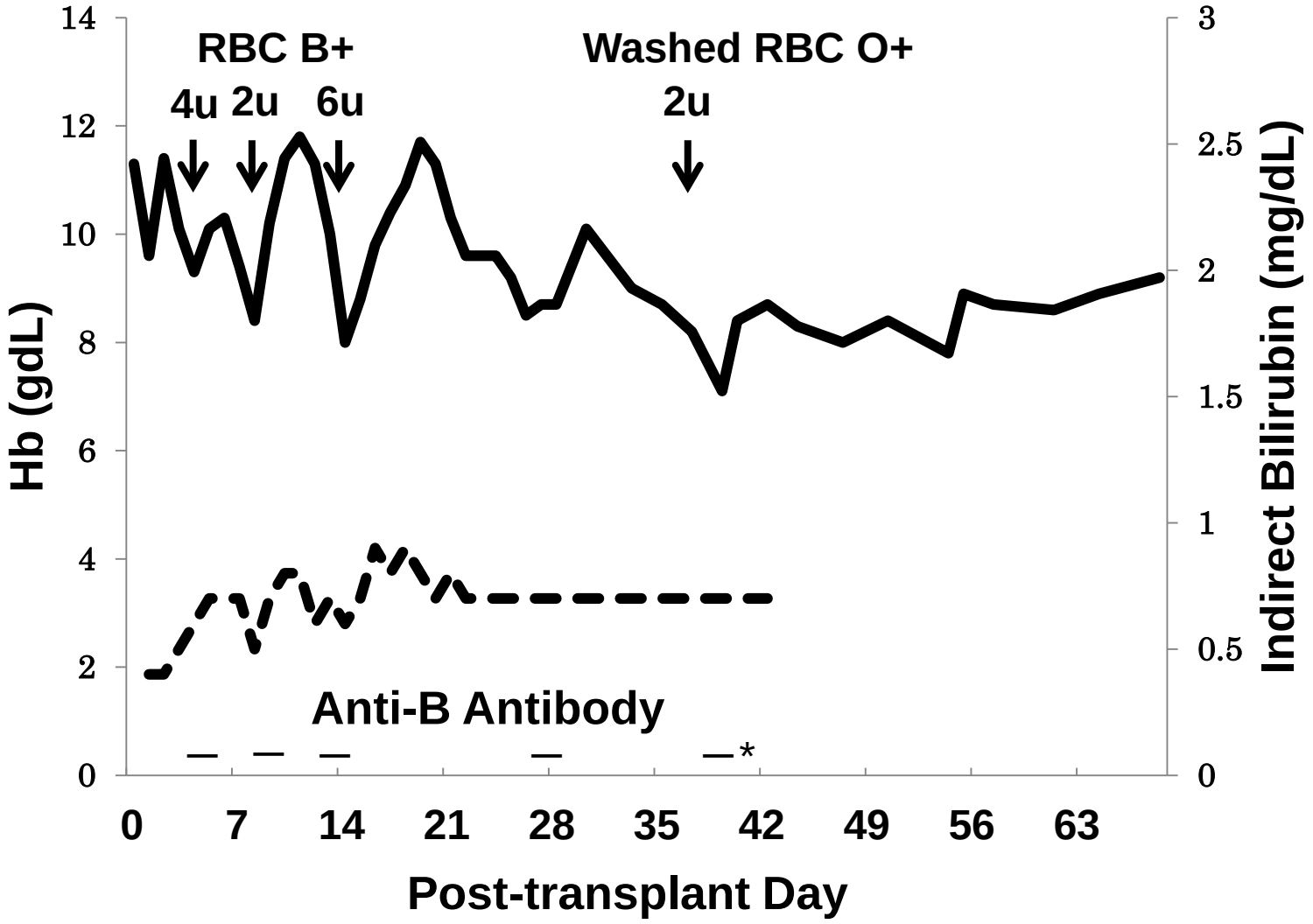
RBC B+
4u 2u 6u
Washed RBC O+
2u
Hb (gdL)
Indirect Bilirubin (mg/dL)
Anti-B Antibody
Post-transplant Day
0
7
14
21
28
35
42
49
56
63
0
2
4
6
8
10
12
14
0
0.5
1
1.5
2
2.5
3

Table 1 Summary of the ABO blood type in LDLLT

	Recipient	Donor 1	Donor 2	Patients
Pediatric	A	O		2
	AB	B		1
	O and B	O		1
Adult	A	O	A	4
	B	O	B	1
	B	O	O	3