Case Report

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Quick Response Code:

Website: www.ajts.org
DOI: 10.4103/ajts.AJTS_54_18

Patient blood management in a patient with multiple red cell antibodies (anti-C, anti-e, and anti-K) undergoing liver transplant in South India: A team approach

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Submission: 24-04-2018
Accepted: 03-03-2019
Published: 24-07-2020

Abstract:

End-stage liver disease (ESLD) patients undergoing liver transplant (LT) surgery are often multiply alloimmunized and pose significant challenges to the transfusion services in terms of red cell cross-match incompatibility, unpredictable blood requirements, and often lead to significant delays in availing compatible red cell units. We report a case of a 64-year-old female from Bahrain, a known case of hepatitis C-related ESLD referred for LT surgery. She had a history of multiple uneventful transfusions in the preceding year. Her blood group was A-positive, direct antiglobulin test, and cold antibodies were negative. Indirect antiglobulin test was positive, and antibody identification confirmed the presence of anti-C, anti-e, and anti-K. Her red cell phenotype was R_2R_2 and Kell negative (C-c+E+e-K-). The patient was started on erythropoietin. Requests for R_2R_2 and Kell negative units were sent to various blood banks across the country. After >800 A/O group units phenotyping and a waiting period of 6 weeks, two compatible R_2R_2 phenotypes and Kell negative could be arranged in-house and three units were received from Gurgaon, North India. Intraoperative management included blood preservation techniques including cell salvage, antifibrinolytic drug, and monitoring using thromboelastography. The estimated blood loss was 350 ml with pre- and postoperative Hb 10.4 gm% and 9.2 gm%, respectively. She received intraoperatively two units of single-donor platelet and four units of fresh frozen plasma and postoperatively one unit of leukocyte-depleted-packed red cells and doing well at 12-month follow-up. This case highlights the importance of advance immunohematology for timely detection of alloimmunization and providing antigen-negative compatible units, proper communication between the transfusion specialists, and the clinical team for proper patient blood management as well as the need for central rare donor registry program to avoid delays in providing compatible blood in such inevitable cases.

Keywords:

Alloimmunization, liver transplant, R_2R_2, rare donor registry, rare group

Introduction

Liver transplantation has provided a favorable change to the outcome of patients with end-stage liver disease (ESLD). These patients are often multiply transfused, alloimmunized, and need proper and timely immunohematological workup to avoid any immune hemolysis-related morbidity and mortality.

Transfusion requirements have been reduced significantly in the past few decades; still,

How to cite this article: Sachan D, Tiwari AK, Dara R, Jothimani D, Kaliamoorthy I, Reddy SM, *et al*. Patient blood management in a patient with multiple red cell antibodies (anti-C, anti-e, and anti-K) undergoing liver transplant in South India: A team approach. Asian J Transfus Sci 2020;14:74-8.

the transfusion therapy for liver transplant (LT) patients remains a challenge in patient with multiple red cell antibodies. We present a case of multiple alloimmunized female patient and her blood management during live-related donor LT (LDLT) surgery.

Case Report

A 64-year-old female from Bahrain, a case of hepatitis C-related ESLD, Child-B cirrhosis. She had a history of multiple episodes of gastrointestinal bleed, encephalopathy, and ascites for the past 12 months requiring frequent interventions in the form of large-volume therapeutic paracentesis. She also had a history of multiple uneventful transfusions and the last transfusion was received from the first-degree relatives around 1-year back. She was referred to our hospital for LDLT. On admission, patient's hemoglobin was 7.5 g/dl, hematocrit – 25%, total leukocyte count – 2230/cmm, platelet – 34,400/cmm, T. bilirubin – 1.06 g/dL, direct bilirubin – 0.12 g/dL, T protein – 6.8 g/dL, albumin – 2.6 g/dL, PT – 16.5 s, and INR – 1.36.

Blood group was A Rh (D) positive. Direct antiglobulin test was negative. Indirect antiglobulin test was performed using commercially available three cell panel (ID Diacell, Biorad) which showed positive agglutination in P1 (3+), P2 (0), and P3 (3+). Antibody identification was performed using 11 cell panels (ID-Diapanel, Biorad) which were suggestive of anti-C, anti-e, and anti-K antibodies. Cold Antibodies were not detected. Extended antigen phenotyping of patient was done using Biorad Rh + K phenotype cards, and the patient was found to be R_2R_2 (C-c+E+e-K-) phenotype. Antibody titer was performed using conventional tube method and using select cells and was anti-e: 1:32, anti-e + C: 1:1024, and anti-e + K: 1:128. On cross-matching, all the units showed incompatibility. The liver team was informed and the search for A or O group, C negative, e negative, K negative, and Rh(D) positive or negative units was initiated. The patient's relatives and children, ten in number who had come to India, were also screened. They were all "A positive," were incompatible with the patient.

Random cross-matching and Rh and Kell phenotyping was initiated in all blood units in our inventory. The segments of blood units were collected from other neighboring blood banks for Rh and Kell phenotyping and cross-matching. Samples were also sent to another hospital Medanta – The Medicity, Gurgaon, and the National Institute of Immunohematology, Mumbai, for confirmation of antibody and requests for compatible units. We also contacted various centers in India for rare donor registry or availability of R_2R_2 and Kell (K)-negative units. More than 500 units among our inventory and other blood banks in the city, only two units could be identified with same phenotype and were compatible.

Meanwhile, the patient was put on erythropoietin and iron therapy to increase the preoperative hemoglobin level. The patient received erythropoietin 4000 units twice weekly for 6 weeks. Folic acid, iron sulfate, and multivitamins were also administered. The hematocrit at the beginning of the treatment was 25%. The hematocrit raised to 28% and 33% after 4 weeks and 8 weeks of treatment respectively.

Three O Rh(D)-positive units with R_2R_2 and Kell-negative phenotype were received from the Department of Transfusion Medicine, Medanta – The Medicity, Gurgaon, North India, (two from their rare-donor registry, one unit from random screening of >300 units in their inventory). The units were collected and transported maintaining cold chain. The transplant was done successfully. The liver graft was obtained from live-donor with blood group "A positive" individual with C+e+K– phenotype.

Before the surgery, the baseline hemoglobin was 10.4 g/dL, platelet count – 44,000/cmm, and INR-1.46. Intraoperative monitoring was done using thromboelastography. Cell saver was also used to salvage the intraoperative blood that was shed. Single-adult dose of tranexamic acid was also administered. Approximate blood loss during the surgery is 350 ml. Two units of single-donor platelet (SDP) and three units of fresh frozen plasma were transfused intraoperatively. No leukocyte-depleted-packed red cells (LDPRC) transfusion was given intraoperatively.

At the end of the procedure, the hematocrit was 9.2 and the patient had no intraoperative complications. During the postoperative period, she had a drop in her hemoglobin and received one unit of LDPRCs and one unit SDP uneventfully. Figure 1 shows hospital course of patient with change in hemoglobin and platelet count and blood transfusions. The intensive care unit and hospital stay were 5 and 16 days, respectively. At discharge, the liver function tests were normal and she is doing well at 12-month follow-up.

Discussion

The present case highlights many important aspects of patient blood management in a multiply alloimmunized patient undergoing LT surgery in India. The case is an excellent example of team approach between transplant surgeons, hepatologist, anesthesiologists, and transfusion specialists across various blood banks in city as well as across the country.

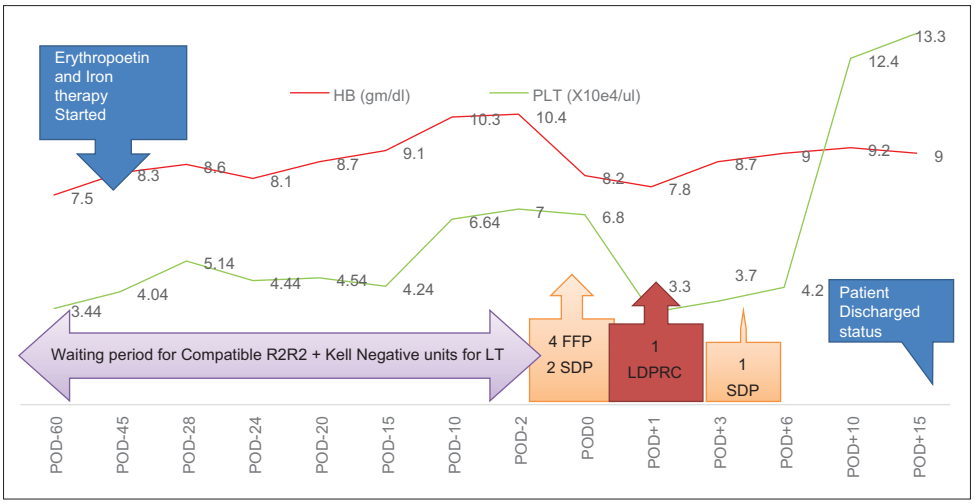

Figure 1: Hospital course of patient waiting for transplant with the trend of hemoglobin and platelet count

From a transfusion specialist point of view, preoperative immuno-hematological workup is critical involving identifying clinically significant alloantibodies, availing antigen-negative compatible blood, and meeting demands of major surgeries such as liver transplantation.

Red cell alloimmunization can lead to several problems varying from delay in getting compatible blood to hemolytic transfusion reactions. The frequency of red cell alloantibodies varies considerably depending on numerous factors, for example, demographics, previous transfusions, pregnancy, genetic constitution, immune status, disease factors, time and frequency of screening, and sensitivity of methodology. UK single-center survey had reported 6.8% clinically significant red cell antibodies in adults undergoing liver transplantation and the most commonly reported alloantibodies in alloimmunized patients are alloantibodies against Rh and Kell antigens.[1] Luzo *et al*. have shown a high incidence of 23% in Sao Paulo, due to ethnic heterogeneity.[2] Studies have also reported the negative influence of the history of red cell antibodies on patient survival after LT highlighting the importance of appropriate patient blood management for alloimmunized patients.[3]

To arrange multiple antigen negative or rare blood group units, there is a need to develop a centralized rare donor database involving voluntary donor organizations as well as reference laboratories and organize the information about rare donors in India. In the era of medical tourism, the centralized donor database will help patients in communities throughout the country and in some cases around the world. In the present case study, two units were sourced from a local registry of around 300 donors maintained by a hospital in Gurgaon. It is desirable to have a national level registry for wider access and shorter turnaround time (TAT). Since we depended largely (three out of five) on typing of units in inventory and to small extent (two out of five) on a local registry, our TAT to arrange the compatible units were over 50 days. Readily accessible large national database could have shortened this TAT, considerably.

Screening of all donors, however, is not often performed due to limiting resources such as antisera, staff, and costs. Some facilities identify rare blood type donors by performing mass antigen screening. At present, there are many studies from India which has shown red cell minor antigen profiles of blood donors and have shown Rh and Kell antigen frequencies as shown in Table 1.[4-13]

However, no much data are available regarding any active registry and follow-up of the typed donors. Knowledge of red cell antigen phenotype frequencies in a population is definitely the first step in understanding the ethnic distribution, in creating a donor data bank for the preparation of indigenous cell panels, and providing antigen-negative compatible blood to patients with multiple alloantibodies. Most transfusion centers rely on random cross-matching and searching in existing inventories; rather than accessing rare donors' registry. Before searching the antigen-negative compatible units, the prevalence of compatible donors should be determined. To calculate the prevalence, the prevalence of donors who are negative for one antigen should be multiplied with the prevalence of donors who are negative for other antigens. For example, if the prevalence of C antigen 85%, e antigen 98%, and Kell Antigen 2%. The prevalence of compatible donors (C negative, e negative and Kell negative, A positive) as in our case would be 0.15 (C-) X 0.02 (e-) X0.98 (K-) = 0.002 or 2 in 1000 donors.

Other strategies include screening of family members, intraoperative blood salvage, and collection and freezing

Table 1: Indian studies showing Rh and Kell prevalence in the Indian donor population

Study	Study population	Number of donors	C %	c %	E%	e %	Kell %	R_2R_2 phenotype
Basu *et al*., 2018[4]	West Bengal	1528	-	-	-	-	0.79	0.72
Pachaury *et al*., 2017[5]	Rajasthan	3014	81.85	62.77	17.25	98.71	-	1.19
Gundrajukuppam *et al*., 2016[6]	Andra Pradesh	1000	88	54.9	18.8	98.4	-	0.7
Garg *et al*., 2015[7]	North India	2769	91.8	55.2	21.1	98.7	1.6	0.8
Kahar and Patel 2014[8]	Gujarat	115	81.74	56.52	21.74	100	6.09	0
Lamba *et al*., 2013[9]	Chandigarh	1000	85.1	62.3	21.5	99	2.8	
Makroo *et al*., 2013[10]	Delhi	3703	87	58	20	98	3.5	0.8
Sharma *et al*., 2013[11]	Central India	1000	84	58.3	25.6	78.5	-	4.7
Agarwal *et al*., 2013[12]	New Delhi	508	-	-	-	-	1.97	0.27
Thakral *et al*., 2010[13]	North India	1240	84.7	52.8	17.9	98.8	5.68	1.45

of autologous blood units when the patient's condition permits.

Preoperative red cell augmentation with erythropoietin, intraoperative cell saver, and postoperative blood conservation through judicious control of laboratory testing should be planned. The use of erythropoietin before surgery allowed us to raise the total red cell mass in our patient. The feasibility of using intraoperative hemodilution and intraoperative red blood cell (RBC) salvage, as well as ways of minimizing hemostatic derangements intraoperatively must be discussed and planned ahead of time. For the transfusion service, this might require reserving additional units of platelets, plasma, and cryoprecipitate for the transplant. Intraoperative blood salvage can also be of benefit in transplant cases with difficult RBC antibodies.[14]

The risk of alloimmunization can be minimized by routine typing the donors and patients for clinically significant antigens. The proactive use of Rh- and K-typed units may prevent some of these patients from being immunized. This extended matching would be an ultimate solution, although the associated logistics and cost will raise the serious concern, especially in resource-limited countries such as India. Due to the different distribution of blood groups in patient and general populations, managing inventory in the face of extended cross-matching further poses serious challenges.

To minimize the risk of hemolysis, alloimmunized patients are often managed with antigen-negative PRBC units for the first 5–10 units when the antibody is still present. They may be switched to antigen-unscreened units during massive blood loss when there is hemodilution of antibody/ies, and switched back to antigen-negative units for the last 5–10 units transfused when transfusion returns to small volumes and transfused cells are expected to remain in the circulation. In patients with multiple antibodies, for whom sufficient quantities of antigen-negative blood cannot be found, consideration is given first to avoid antibodies that fix complement with the potential to cause intravascular hemolysis.[15,16] However, the time to switch back to the use of compatible blood is not always clearly delineated, potentially putting the patient at risk for a delayed hemolytic transfusion reaction, and increased postoperative morbidity.

Most unusual alloantibodies are predicted to cause shortened red cell survival, but transfusion of incompatible blood may or may not result in clinical or laboratory signs of hemolytic transfusion reaction. A balance is required between pretransfusion estimation of clinical significance and search for expensive and rare phenotype blood for patients with alloantibodies to high-incidence antigens or multiple antigens. In India, RBC survival studies or cellular assays (e.g., the monocyte monolayer assay and chemiluminescence test) are not widely developed which can aid in the decision to transfuse RBCs incompatible with antibodies to high-incidence antigens.

Still, situations like this can lead us in a near but not impossible situation where we are forced to think about the need of centralized (and not just local) registry of donors with rare antigen profile.

The transfusion medicine has advanced significantly in the past few years preventing many hemolytic reactions by timely antibody screening and providing antigen-negative and compatible units. Complete screening of alloantibodies combined with rational blood transfusion policy is mandatory to prevent RBC alloimmunization among LT candidates. We recommend the transfusion of Rh and Kell antigen-matched blood to patients with high transfusion requirements in the future and enforce the need to have a national donor registry for rare blood groups.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will

be made to conceal their identity, but anonymity cannot be guaranteed.

Acknowledgments

The authors express thanks to all staff in the Department of Transfusion Medicine, Gleneagles Global Health City, Medanta – The Medicity, Gurgaon, the National Institute of Immunohematology, and various Chennai blood banks for their greatest cooperation and technical assistance for finding rare units among inventory.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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