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Development of Non-ABO Red Blood Cell Alloantibodies in Patient Undergoing Allogeneic Haematopoietic Stem Cell Transplant

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Abstract

Alloantibodies that are non ABO Alloimmunization to protein antigens happens only after exposure, in contrast to ABO isohaemagglutinins, which are present naturally, even in the absence of prior exposure. It is recognized that while non-ABO RBC antibodies are less common than ABO antibodies, they generate essentially the same issues that lead to unfavorable clinical results. If non-ABO alloantibodies are identified early on, these issues related complications may be avoided This call for an in-depth understanding of the recipient and donor's ABO-Rh grouping, antibody screening, and the phenotype of certain antigens. Equally important, the temporal association time between transplantation and hemolysis can help identify the underlying mechanism of hemolysis and direct appropriate management. Therefore, for that, it is crucial to identify the etiology of post-HSCT anemia for prevention and therapy, in addition to a thorough grasp of the mechanism of anemia in non-ABO-incompatible HSCT and the temporal link between HSCT and anemia. Finding the cause of post-HSCT anemia is essential for prevention and therapy, in addition to a thorough grasp of the mechanism of anemia in non-ABO-incompatible HSCT and the temporal link between HSCT and anemia. Therefore, for that, it is crucial to identify the etiology of post-HSCT anemia. In this case report review, we would like to highlight the vital role of transfusion medicine services and stem cell clinical teams in paying particular attention

to the clinical significance of non-ABO alloantibodies involved to avoid causing overt hemolysis of incompatible donor RBCs or delayed erythropoiesis. Considering the fact that some of the Haematopoietic stem cell transplant centers do not give an attention to the other non-ABO RBC antigens.

Keywords

Haematopoietic Stem Cell Transplant (HSCT), Non-ABO Red Blood Cell Antibodies, Alloantibodies

1. Introduction

The majority of patients undergoing hematologic disorders are on long-term transfusion programs. Therefore, alloantibodies may develop due to transfusion of not phenotype matched RBC may cause auto- or alloimmunization in patients after allogeneic hematopoietic stem cell transplantation (HSCT). Consequently, engrafting process of hematopoietic stem cells may be impacted by developed alloantibodies against patients' red blood cells. The presence of antibodies against red blood cells other than ABO antibodies in patients undergoing allogeneic transplantation is not common since high-dosechemo radiotherapy with allogeneic Haematopoietic stem cell transplant is routinely used as therapy for patients with hematologic malignanciesthe detection of non ABO-antibodies is essential to determine the most suitable donor. In some cases, a patient who has been known to be negative for antibodies may develop an antibody any time post Haematopoietic stem cell transplant. For that, the close monitoring is essential. The purpose of this case report is to highlights the need for ongoing vigilance for patients who will have stem cell transplant and have a history of non-ABO antibody [1].

In some cases, non-ABO antibodies develop for unknown reasons. The regimen administered before HPC transplantation has the aim of eliminating the patient is underlying disease and completely eradicate the host's immune response [2]. The appearance of hemolytic anemia due to anti-A and anti-B antibodies in patients undergoing Haematopoietic stem cell transplant has been widely observed. DAT result after major or minor ABO-mismatched transplant must be considered if positive as a sign of antibody development or a sign of early rejection [3]. With different types of hematological disorders, the basic blood bank laboratory tests that include ABO-Rh and antibody screen should be performed. According to a review article, the incidence of immune hematologic problems associated to non-ABO blood group mismatch following HSCT is 10%, which likely reflects underreporting [4].

2. Case Report

A 35-year-old male with sickle cell anemia was admitted to King Abdulaziz Medical Cityat National Guard for a stem cell transplant; the patient was expe-

riencing severe renal injury and had undergone a red blood cell exchange two years prior. Tests conducted in the laboratory revealed the following results: Hgb 112 (120 - 160 gm/L) , Hct 0.338 (0.36 - 0.54 L/L) and blood group B Positive with negative antibody screening, and no blood transfusion requests were made at this time. The adult stem cell transplant center determined that the donor is the patient's sister, who had the same blood type as the patient and was B Positive. The patient was transfused six units of red blood cells one week before the transplant to manage vaso-occlusive crises. All transfused units are match with the patient regarding Rh and K phenotype and all units were sickle cell tests negative and normal G6PD. Following the red blood cell exchange, the Hct was 0.30 (0.36 - 0.54 L/L 4 and Hgb was 102 (120 - 160 gm/L). Later one the patient was admitted for stem cell transplantation with the following laboratory results were obtained: Hgb 76 (120 - 160 gm/L) and Hct was 0.228 (0.36 - 0.54 L/L) a new sample for blood grouping **Table 1** and antibody screening were received two days prior to the scheduled stem cell transplant, where The antibody screening resulted in a positive result (**Figure 1**), and further investigations revealed that anti-E alloantibody was detected (**Figure 2**) in a pre-transplant compatibility test, confirming the/alloantibody's persistence despite immunosuppression. Standard serological techniques were used to identify the antibody, and prolonged phenotyping of the patient's erythrocytes. However, one year after transplantation, a routine type and screen was received where it revealed a negative antibody screen with a positive (DAT) direct antiglobulin test (**Table 2**) indicating the presence of antibodies bound to the erythrocytes. The elution technique was carried out and anti-E was detected in the Eluate (**Figure 3**).

Table 1. Type and screen with the patient sample.

Type and Screen Test by Solid Phase Technique						
Forward grouping				Reverse Grouping		Interpretation
Anti-A	Anti-B	Anti-D	Rh Cont.	A1 Cells	B Cells	
0	**4+**	**4+**	**0**	**3+**	**0**	**B Positive**

CAPTURE-R READY- SCREEN (3)
MASTER LIST

IMMUCOR, INC. Norcross, GA 30071 USA
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EXPIRES: 2022/06/21

CELL		Rh-Hr						Kell						Duffy		Kidd		Lewis		P1	MN				Lutheran		Xg	PATIENT RESULT
	DONOR	D	C	c	E	e	Cw	K	k	Kpa	Kpb	Jsa	Jsb	Fya	Fyb	Jka	Jkb	Lea	Leb	P1	M	N	S	s	Lua	Lub	Xga	
I	R1Wr1 B4245	+	+	0	0	+	+	0	+	0	+	0	+	0	+	+	+	0	+	0	+	0	+	0	0	+	+	0
II	R2R2 C6889	+	0	+	+	0	0	0	+	+	+	0	+	+	0	0	+	0	+	+	+	+	0	+	0	+	+	1+
III	rr G1416	0	0	+	0	+	0	+	+	0	+	0	+	+	0	+	0	+	0	+	+	0	+	0	0	+	+	0
	Positive Control	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	4+

Figure 1. Antigram showing results of Antibody screening 3-cell panel.

Table 2. Direct antiglobulin test.

DAT	DAT Control cells	Interpretation
2+	3+	Positive

CAPTURE-R READY- ID
MASTER LIST

IMMUCOR, INC. Norcross, GA 30071 USA
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EXPIRES: 2022/07/19

CELL		Rh-Hr						Kell						Duffy		Kidd		Lewis		P1	MN				Lutheran		Xg	PATIENT RESULT
	DONOR	D	C	c	E	e	Cw	K	k	Kpa	Kpb	Jsa	Jsb	Fya	Fyb	Jka	Jkb	Lea	Leb	P1	M	N	S	s	Lua	Lub	Xga	
1	RzR1 A3355	+	+	0	+	+	0	0	+	+	+	0	+	+	+	0	+	+	0	0	0	+	+	+	0	+	+	0
2	R1Wr1 B10314	+	+	0	0	+	+	0	+	0	+	0	+	0	+	+	+	+	0	+	+	0	+	0	0	+	+	0
3	R2R2 C5901	+	0	+	+	0	0	0	+	0	+	0	+	+	+	+	+	0	+	+	+	+	+	+	0	+	+	2+
4	Ror D2465	+	0	+	0	+	0	0	+	0	+	0	+	0	0	+	+	0	0	+	+	+	0	+	0	+	+	0
5	r'r E988	0	+	+	0	+	0	0	+	0	+	0	+	0	+	+	+	0	+	+	+	+	+	0	0	+	+	0
6	r''r F730	0	0	+	+	+	0	0	+	0	+	0	+	+	+	+	0	+	0	+	+	+	+	+	0	+	+	1+
7	rr H1049	0	0	+	0	+	0	0	+	+	+	0	+	+	0	0	+	0	+	+	+	+	0	+	+	+	+	0
8	rr G1784	0	0	+	0	+	0	+	+	0	+	0	+	0	+	+	+	0	+	+	0	+	0	+	0	+	+	0
9	rr H1581	0	0	+	0	+	0	0	+	0	+	0	+	+	0	+	0	0	+	0	+	+	0	+	0	+	0	0
10	rr N3185	0	0	+	0	+	0	0	+	0	+	0	+	0	+	+	0	0	+	+	0	+	0	+	0	+	+	0
11	rr G1881	0	0	+	0	+	0	+	+	0	+	0	+	0	+	0	+	0	+	0	0	+	0	+	0	+	+	0
12	rr H1515	0	0	+	0	+	0	0	+	0	+	0	+	+	0	+	0	0	+	0	+	0	+	0	0	+	+	0
13	rr V185	0	0	+	0	+	0	0	+	0	+	+	+	+	0	+	+	+	0	+	+	+	0	+	0	+	0	0
14	R1R1 B9059	+	+	0	0	+	0	0	+	0	+	0	+	+	0	0	+	+	0	+	+	0	0	+	0	+	0	0
15	Positive Control	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	4+
16	Negative Control	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	0

Figure 2. Antigram showing results of antibody identification 16 cell panel.

CAPTURE-R READY- ID
MASTER LIST

IMMUCOR, INC. Norcross, GA 30071 USA
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LOT NO: E449
EXPIRES: 2023/06/20

CELL		Rh-Hr						Kell						Duffy		Kidd		Lewis		P1	MN				Lutheran		Xg	PATIENT RESULT	
	DONOR	D	C	c	E	e	Cw	K	k	Kpa	Kpb	Jsa	Jsb	Fya	Fyb	Jka	Jkb	Lea	Leb	P1	M	N	S	s	Lua	Lub	Xga	ELU	LW
1	RzR1 A3355	+	+	0	+	+	0	0	+	0	+	0	+	0	+	+	0	0	+	+	+	0	+	+	0	+	+	3+	0
2	R1Wr1 B10314	+	+	0	0	+	+	+	+	0	+	0	+	+	+	0	+	0	+	+	+	+	+	+	0	+	+	0	0
3	R2R2 C5901	+	0	+	+	0	0	0	+	0	+	0	+	0	+	+	+	0	0	+	+	0	+	+	0	+	+	4+	0
4	Ror D2465	+	0	+	0	+	0	0	+	0	+	0	+	0	0	+	+	0	0	0	0	+	0	+	0	+	+	0	0
5	r'r E988	0	+	+	0	+	0	0	+	0	+	0	+	0	+	+	+	0	+	+	+	+	+	0	0	+	+	0	0
6	r''r F730	0	0	+	+	+	0	0	+	0	+	0	+	+	+	+	+	+	0	+	+	+	+	+	0	+	+	4+	0
7	rr H1049	0	0	+	0	+	0	0	+	0	+	0	+	+	+	0	+	+	0	+	+	0	+	0	0	+	+	0	0
8	rr G1784	0	0	+	0	+	0	+	+	0	+	0	+	0	+	0	+	0	+	+	0	+	0	+	0	+	+	0	0
9	rr H1581	0	0	+	0	+	0	0	+	+	+	0	+	+	0	0	+	0	+	+	+	+	0	+	+	+	+	0	0
10	rr N3185	0	0	+	0	+	0	0	+	0	+	0	+	+	+	0	+	0	0	+	0	+	0	+	0	+	+	0	0
11	rr G1881	0	0	+	0	+	0	0	+	0	+	0	+	+	0	+	+	+	0	0	0	+	+	+	0	+	0	0	0
12	rr H1515	0	0	+	0	+	0	0	+	0	+	0	+	0	+	0	+	+	0	+	0	+	0	+	0	+	+	0	0
13	rr V185	0	0	+	0	+	0	+	0	0	+	0	+	+	0	+	0	0	+	+	+	0	+	+	0	+	0	0	0
14	R1R1 B9059	+	+	0	0	+	0	0	+	0	+	0	+	+	0	+	0	0	+	0	+	+	0	+	0	+	+	0	0
15	Positive Control	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	4+	4+
16	Negative Control	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	/	0	0

Figure 3. Antigram showing results of elution identification 16 cell panel.

3. Materials and Methods

For the pre-transfusion tests, a full 7 ml tube with lavender cap is required to perform forward (cells) and reverse (plasma) grouping, antibody screening and compatibility testing. The validity of the type and screen sample is 72 hours post

collection. If a patient is ABO Rh group history is unknown, the blood bank will obtain two separate types and screen samples. These samples will be submitted to the transfusion services for pre-transfusion and compatibility testing. All specimens must be tested for ABO group and Rh type to determine the patient's blood group, and for the presence of unexpected antibodies to red blood cell antigens using the antibody-screening test. Prior to blood transfusion, the ABO and D blood groups of patients are determined twice, in two independently collected samples.

Whole blood samples were collected by venipuncture into an EDTA tube (BD Vacutainer K2E EDTA, 7 mL, 10.8 mg). Samples were then centrifuged at 4800 rotation per minute (rpm) for 10 minutes to separate plasma from the red blood cells at room temperature, which can then be stored at 2˚C - 10˚C for 14 days. ABO forward and reverse grouping and Rh antigen phenotyping were performed automatically using the Neo system (Immucor Inc., Norcross, GA, USA). Neo Iris™ uses a microplate-based platform to automate standard Immunohematology assays which include ABO grouping and Rh (D) typing, antigen screening and antibody screening and identification. Neo is a microprocessor-controlled device designed for the complete automation of immunohematology in vitro diagnostic tests using human blood. The NEO automates test processing, interpretation and data management. Antibody screens and initial antibody identification were performed according to the instructions of the manufacturer of the Capture c ® Ready Screen® and Capture R® Ready ID® (Immucor Inc., Norcross, GA, USA). Both tests were performed on the same automation device. Secondary ABO/RhD grouping was performed using conventional tube technique (Immucor Inc., Norcross, GA, USA). The direct antiglobulin test (DAT) was performed using the automation system on the ECHO of the Capture-c ®Select (Immucor Inc., Norcross, GA, USA) and Elution on DAT-positive sample was performed using "Acid elution" method.

4. Discussion

Non-ABO red blood cell alloantibodies are antibodies that are produced in response to antigens present on RBCs from genetically different individuals. Moreover, non-ABO may be allo- or auto-antibodies and anemia that results from ABO incompatibility is still a significant contributor to post-HSCT immune-mediated anemia and does not lessen the significance of those antibodies Hemolysis. The systemic inflammation can result from transfusion responses brought on by these antibodies. Following allogeneic hematopoietic stem cell transplantation, anemia may be caused by the immune system or by other factors that non-immune-mediated. Severe anemia caused by non-ABO blood types typically includes the humoral arm immunological response. Therefore, the Engraftment failure on the HSCT level can be brought on by non-ABO antibody-induced anemia [5]. However, RhD antigen is the most potent non-ABO antigen, followed by K antigen and Additional alloantibodies are more likely to develop in

patients with a history of alloimmunization [6]. In general, The RhD antigen is the most commonly linked non-ABO RBC antigen to the onset of post-BMT alloimmune hemolytic anemia [7]. A cause has been reported where a severe hemolytic anemia due to mismatch of the JK antigen system. Patients undergoing allogeneic HSCT and were on chronic transfusion therapy are typically at higher risk of developing auto- and alloimmunization [8]. Depending on the timing of antibody generation, donor and recipient, or both and the source of RBC alloimmunization may arise by non-ABO mismatch. Therefore, pre-existing antibodies in the graft as well as newly developed antibodies by passenger or engrafted cells are examples of donor-derived alloantibodies. Nevertheless, preexisting antibodies as well as antibodies generated by remaining lymphocytes and plasma cells are examples of recipient-derived alloantibodies [9].

Non-ABO RBC alloantibodies can potentially result in acute transplant failure, which in certain situations remains a devastating complication with very poor outcomes. In our case, this patient was cleared to have a hematopoietic stem cell transplant and had no prior history of antibodies. However, during the conditioning phase, a 3-cell panel antibody screening revealed a positive result, as illustrated in **Figure 1**. The anti-E antibody's apparent specificity was then demonstrated by the antibody identification using the 11-cell identification panel, as shown in **Figure 2**, and DAT was negative (**Table 3**) Despite the patient received RHK phenotype matched red blood cells, but he developed anti-E because he received blood outside the facility.

After ten months following the stem cell transplant, a sample was obtained for type and screen; the results were found to be consistent with the previous history of antibodies. Interestingly, the direct antiglobulin test (DAT) was positive and the eluate results revealed the presence of an autoanti-E and **Table 2** and **Figure 3** respectively. Non-ABO RBC alloantibodies can develop after stem cell transplantation and are influenced by the donor and recipient incompatibility as well as the antigen specificity of the antibody. Antibodies can develop at any time following stem cell transplant. However, most post stem cells patients experience the development of antibodies within the first year following transplantation. In actuality, a patient may generate RBC antibodies while being immunosuppressed [10].

In 2018 there was a published a retrospective study indicated that there was a limited information regarding the specificity of immune status and risk factors for the developed of non-ABO alloantibodies and the study was aimed to identify antibody specificities, risk factors and clinical significance of the development of RBC allo-antibodies in HSCT patients. The authors analyzed the data in this study and reached that 1314 donor/ recipient pairs were analyzed. So, among of

Table 3. Direct antiglobulin test.

DAT	DAT Control cells	Interpretation
0	3+	Negative

those patients 110 (13%) of patients developed RBC alloantibodies, 66 patients (5%) prior to HSCT, and 103 (8%) developed the first RBC alloantibody after HSCT. 8 patients (0.6%) with an RBC alloantibody before HSCT developed further RBC alloantibodies after HSCT. Most patients developed only one RBC alloantibody but in single patients up to 6 antibodies could be detected. For this reason, the potential donor should be subjected for phenotype of corresponding antibody and the negative antigen should be selected as the suitable donor [11]. Certainly, there are limited data on how non-ABO alloantibodies affect HSCT outcomes in patients with thalassemia. Relatively little attention has been paid to non-ABO system antibodies, with the majority of publications in the literature are focusing on transfusion reactions rather than on any putative role in in allograft rejection. Conversely, a published study noted that while engraftment and survival outcomes were unaffected, the incidence of antibody generation is probably influenced by excessive exposure to transfusions and the creation of a novel red blood cell antibodies [12]. Most RBC allo-antibodies appear to be induced by RBC transfusion rather than by minor blood group mismatching between donor/recipient pairs and this is because of red blood cell (RBC) depletion procedure which is considered as a standard technique prior to stem cell or bone marrow transplantation of major ABO-incompatible. RBC alloimmunization rates in sickle cell disease patients range from 23.8% to 45.7%, despite leukoreduction and preventive antigen matching [14]. Hemolysis from non-ABO-incompatible allografts might significantly exacerbate the post-BMT phase, posing challenging clinical treatment problems [13].

There was a reported case of severe immune hemolytic anemia due to multiple RBC alloantibodies after an allogeneic bone marrow transplant the most interesting is the time of appearance and the specificity of the antibodies was strongly suggesting that they were produced by residual recipient lymphoid cells. [14]. After receiving an allogeneic bone marrow transplant, a case of severe immunological hemolytic anemia caused by numerous RBC alloantibodies was documented. The time of manifestation is the most intriguing aspect, and the specificity of the antibodies clearly implies that they were generated by lymphoid cells that were left over from the recipient. Severe hemolytic anemia following an allogeneic bone marrow transplant that is incompatible with ABO as a result of several red cell alloantibodies [15].

5. Conclusion and Future Directions

We can confirm from this case report that non-ABO antibodies ought to be taken into account and given greater weight in transplantation facilities and more prospective study is required to identify the key characteristics of the non-ABO alloantibody in patients receiving stem cell transplantation and to highlight its importance in order to more precisely determine the rate of new post-HSCT alloantibody development and the duration of alloantibody persistence or disappearance in allo-HSCT recipients. In our facility, ABO and antibody screening testing are to be repeated every 3 days, as indicated on all post-stem cell trans-

plant samples as well as documenting any potential blood group conversion or any changes in antibody screening status. When a patient's stem cell transplant sample demonstrates the existence of non-ABO antibody, we strongly recommend thorough pre-transplant donor and recipient screenings. As a result, if potential recipient has history of non-ABO antibody, the transplant team usually send out a number of donors, phenotyping of these donors, and based on the phenotype results, donor with antigen-negative phenotypes corresponding to alloantibodies will be selected as potential donor. Furthermore, the application of extended genotype RBC matching in clinical practice is growing. On the other hand, due to the intricacy of immune-mediated anemia close post-transplant immunohematology monitoring in those patients and this it requires a multidisciplinary collaboration between healthcare professionals with expertise in transfusion medicine, hematology, oncology, and transplantation.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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