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Original Article - Case Study

An Interesting Case of Blood Group Switch after Breast Cancer Therapy

*Meher Ayyazuddin *, Qudsia Umaira Khan **

CMH Lahore Medical & Dental College Lahore, Lahore, Pakistan

**Corresponding authors*: *Meher Ayyazuddin* and *Qudsia Umaira Khan*, CMH Lahore Medical College and Institute of Dentistry, Abdur Rehman Road, Lahore Cantt, Pakistan; Emails: meherayyaz@hotmail.co.uk and drqudsia@yahoo.com respectively.

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ABSTRACT

Blood groups are determined by specific antigens attached to red blood cells that are either carbohydrate or protein in nature. Changes in gene expression encoding for various blood types are rare, with the ABO blood group antigen most commonly altered. We report a female patient whose blood group changed from A, Rh positive to A, Rh negative, over the period of 10 years (1999-2009). During this time period, she was diagnosed with breast carcinoma and a lumpectomy was performed, followed by chemotherapy (with anthracycline and docetaxel) along with local irradiation. There has been no remission after recovery. It was noticed that the patient's blood group had changed. A possible reason may be Rh mosaicism and a mutation in the Rh gene, resulting in the alteration of Rh antigen expression. The reason causing this mutation is unclear. However, in some cases changes in blood groups are related to patients' chemotherapy treatment and their remission status.

Keywords

Breast cancer, infusion reaction, docetaxel, blood groups, blood group switch, Rh antigen, Rhesus antigen.

Abbreviations

Red blood cells (RBC); white blood cells (WBC); acute myelogenous leukemia (AML); chronic myelogenous leukemia (CML); rhesus (Rh).

INTRODUCTION

Blood is a principal part of the vascular system of human beings acting as a vehicle for transport of respiratory gases, nutrition, metabolites and waste products. It is comprised of red blood cells (RBC), white blood cells (WBC) and platelets suspended in a fluid called plasma. A blood group is identified by its antigens and antibodies. RBCs are marked by antigens, which are either sugars or proteins attached to their membrane. RBC antigens are inherited traits and their expression generally remains constant throughout the life of an individual[1].

A change in one's blood group is a rare occurrence, in which the genes encoding the ABO blood group antigens possibly undergo a mutation causing a change in antigen expression. Loss or diminished expression of RBC antigens has been reported in association with both solid tumors and hematological malignancies. ABO blood group antigen is the most commonly altered blood group antigen[1]. In some cases, a change in blood group of an individual is determined by the treatment with chemotherapy and his/her remission status[2]. Combinations of anthracycline and taxanes (docetaxel) have been widely used in breast cancer therapy. However, along with high responses rates, chemotherapeutic drugs, such as docetaxel, also have adverse effects. Docetaxel is one of the cytotoxic agents that frequently triggers acute infusion reactions. These reactions typically occur within minutes or hours of drug administration, with

characteristic symptoms including "standard" reactions of flushing, itching, dyspnea, hypoxia, fever and "classical hypersensitivity" reactions[3,4].

A type of change that occurs less frequently is the Rh blood group change characterized by the presence of two populations of red blood cells of different Rh phenotype (Rh mosaicism) in the blood from patients suffering from acute and chronic myelogenous leukemia (AML, CML), myeloid metaplasia, polycythemia or myelofibrosis. Somatic mutations can result in Rh mosaicism causing a rise in production of an abnormal clone of precursor cells, which can occasionally disappear during remission and return to normal Rh phenotype[5,6].

Another potential reason for blood group discrepancies can be chimerism. A chimera exists when two or more distinct cell populations containing genetic material from more than one zygote exist within an individual[7]. However, Rh mosaicism was also observed in healthy individuals in which the possibility of chimerism was eliminated but it is not clear as to what causes changes in Rh blood group[8]. Herein, we report a female patient, with a history of breast cancer and therapy, who experienced a change in Rh blood group over a period of 10 years.

CASE REPORT

In 2006, a 36-year-old woman was diagnosed with stage two squamous cell breast carcinoma. A malignant tumor, spread within a 5 cm radius, was found in her left breast. Her blood grouping was performed during her previous two pregnancies in 1999 and 2002 respectively, as part of a routine checking procedure. The blood group was found to be A, Rh positive in both cases. The patient had no family history of breast cancer. The oncologist planned surgical intervention. A lumpectomy was performed soon after the diagnosis and blood grouping determined again. It was A, Rh positive. A blood transfusion was not required. The patient received further treatment which included 8 cycles of induction chemotherapy, each after a three-week interval, succeeded by 20 cycles of radiotherapy. The chemotherapy treatment plan included 4 cycles of anthracycline, followed by 4 cycles of docetaxel. However, the patient had a severe infusion reaction in the 5th session of chemotherapy, which was the first with docetaxel. The main symptoms included burned skin and high-grade fever. Usage of docetaxel was discontinued. After the patient had survived the reaction, she was given anthracycline in the 6th cycle and with that, her chemotherapy treatment concluded (Table 1). There is no history of remission afterwards. In 2009, during her third pregnancy, her blood grouping was determined once again and it had changed to A, Rh negative. Testing was repeated thrice, confirming the blood group was A, Rh negative.

METHOD

Mandatory blood typing takes place at the time of pregnancy or blood transfusion in order to ensure compatibility between the donor and recipient blood groups. The routine clinical analysis carried out in the aforementioned case included the reverse forward grouping mechanism using micro-plating technology, along with the slide test (Table 2).

Table 1. Brief summary of the patient's diagnosis and interventions

Features	Case
Age	36
Gender	Female
Diagnoses	Breast cancer
Surgical i**ntervention** (May 12, 2006)	Lumpectomy
Induction chemotherapy (2006)	4 shots anthracycline 1 shot docetaxel 1 shot anthracycline

Table 2. History of the blood group determination tests

Blood Group Determination	Method	Results
1999	Slide Test	A, Rh positive
2002	Slide Test	A, Rh positive
2006	Reverse & Forward	A, Rh positive
2009 (3 tests)	Reverse & Forward	*A, Rh negative*
2020	Reverse & Forward	*A, Rh negative*

Forward grouping requires a blood sample and suggests the presence or absence of A, B and RhD antigens in RBCs, whereas reverse grouping indicates the presence or absence of anti-A, anti-B and anti-D antibodies in serum. In forward grouping, blood cells are placed in test tubes along with saline as a diluent media, and then one drop of each anti-A, anti-B and monoclonal IgM anti-D antibodies are separately added within these samples. These tubes are subjected to centrifugation for few minutes, and then, the resultant matrix is gently shaken for observing agglutination. The purpose of centrifugation is to ensure enhanced chemical interactions, particularly for weaker antibodies to react, thus leading to agglutination[9].

Similarly, reverse grouping can be performed using the blood serum, which is treated against RBC reagent groups of A, B and RhD. The subsequent agglutination patterns are monitored. However, microplate technology is a faster and more sensitive method of typing analysis with the feasibility of automation. In this technique, both antibodies in blood plasma and antigens on RBCs can be determined. Typical microplates consist of a large number of small tubes that contain a few µL of reagents, which are treated against the blood samples. Following centrifugation and incubation, the subsequent agglutination can be examined by an automatic read out device[9]. If automated techniques result in any blood typing discrepancies, manual methods are performed. which include the tube or slide test. At times, results obtained automatically are confirmed again through manual technique[10].

However, whilst Rh typing, the phenomena of weak D and partial D variants should be kept in mind[11]. For pregnant women is recommended double testing, unless samples are tested on secure automation, by direct agglutination with potent IgM monoclonal anti-D. These reagents are selected to detect all except the weakest D variants and to give a negative reaction with DVI red cells. Consequently, patients who have the DVI phenotype and are, therefore, likely to make anti-D, are typed as D negative and treated as D negative for blood transfusion and administration of anti-D immunoglobulin during pregnancy and following delivery of a D positive baby. Patients with very weak expression of D, including those with DEL phenotype, will also be typed as D negative. DVI and DEL are weak forms of D[11,12].

DISCUSSION

We reported a female patient without any history of blood transfusions or of remission of a malignant tumor. The infusion reaction incident with docetaxel usually causes symptoms associated with hypersensitivity or allergic reactions. These are attributed mainly to cytokine release and mast cell/basophil activation, respectively. Even with precautionary premedication with glucocorticoids and antihistamines prior to infusion, approximately 2% of patients will experience potentially life-threatening reactions. Even though combinations of anthracycline and docetaxel generate high response rates, they are associated with a higher toxicity rate[13,14]. However, we do not know whether the change in Rh blood group is due to the chemotherapy process itself. This is yet to be investigated in detail.

A possible explanation is that chemotherapy might affect the Rh antigens or the antigens of ABO blood group, which are comprised of complex carbohydrate molecules. Two glycosyl transferase enzymes are encoded by the genes of the ABO blood group. Both these enzymes alter the molecules of carbohydrates of the ABO blood group antigens on

surface of RBCs and play a vital role in the determination of the blood group of any individual[15].

There is a common precursor substance that leads to the formation of A, B and H antigens. L-fucose is added to terminal galactose with the help of H-transferase and the second enzyme is A or B transferase, which adds N-Acetyl galactosamine or galactose to the H substance[16]. In hematopoietic diseases, there are two possible mechanisms that are responsible for the weakening of the ABO blood group antigen. The first mechanism is the inactivation of A or B transferase and the second is the inactivation of H-transferase. As a result of the first mechanism, expression of the H antigen would increase whereas expression of A and B antigens would decrease due to failure of conversion of the H antigen into A or B. the second mechanism would result in decreased production of H substance, thus causing a subsequent decrease in A and B antigen formation[17].

Several studies revealed that there is a modification in the blood group of some patients after chemotherapy. The results of a study in Denmark showed that the blood group of a female patient transformed from RhD positive to RhD negative over the period of three years. During this period, the patient was treated with local irradiation as well as mastectomy for low-grade persistent breast cancer. She was diagnosed with CML two years later for which she received chemotherapy. Her blood group had changed to O, RhD negative from O, RhD positive after chemotherapy[8]. Although most people are either D positive or D negative, there is a plethora of D variants often categorized as weak D or partial D[11]. However, in her case there was no discrepancy in judging the blood group.

According to the southern blot analysis, it was revealed that the patient was heterozygous at *RH* gene locus. She was carrying two haplotypes, one with the *RHD* gene and the second one with the *RHCE* gene. The *RHD* gene showed a single nucleotide deletion (G600) that caused a frameshift and resulted in a premature stop codon. The second haplotype was normal. The gene deletion was found only in the myeloid lineage according to further analysis. Hence, suggesting that a somatic mutation occurred, since it was found in erythroblasts and pure neutrophils from the peripheral blood, but not in a B-lymphoid cell line derived from the patient. Most probably, this mutation occurred in a stem cell common to all myeloid lineages. However, the possibility of this mutation being inherited cannot be eliminated since genomic analysis of other haemopoietic cell lines and of family members of this patient were not carried out[8].

Although there are many other mutated *RHD* genes and hybrid genes responsible for D phenotypes, they are relatively rare and the most common D genotypes are homozygosity or compound heterozygosity for an *RHD* deletion, *RHD*Ψ*, or *RHD-CE-D*. *RHD*Ψ* is an inactivated *D* gene due to a 37 base pair duplication in exon 4, resulting in a reading frame shift and a nonsense mutation in exon 6[18]. Some *RHD–CE–D* hybrid genes produce no D antigen and include exons 1, 2, 9, and 10 derived from *RHD*, and exons 4–8 derived from *RHCE*. When the subject of D variants arises, mainly two types of molecular mechanisms are responsible. Firstly, one or multiple nucleotide changes in *RHD*, resulting in amino acid substitutions in the RhD protein. Secondly, the product of genetic recombination giving rise to an *RHD–CE–D* gene will also result in D variants[11].

Two further cases were reported in India whose blood groups changed during their treatment. The change in blood groups of both patients was determined by the remission status of their disease. The first patient was suffering from AML and his blood group at the start of treatment was O, Rh positive. His blood group changed to A, Rh negative during remission. The blood group of the patient was altered after only two cycles of induction chemotherapy and remained the same while the patient continued to be in remission[2].

The other patient had acute lymphoblastic leukemia and his blood group was reported to be B, Rh negative. His relapse caused his blood group to change to B, Rh positive but it reverted back a month later to B, Rh negative after receiving chemotherapy. However, the patient's blood group changed back to B, Rh positive two months later[2].

These changes in the ABO blood group antigens reflect the presence of malignancy. The blood group can be converted to the original upon remission and there may be suppression in the blood group antigens with the relapse of the disease[1]. These cases are mentioned to educate field professionals about the alteration of ABO genes in cancer patients throughout their chemotherapy treatment.

CONCLUSION

Here we can deduct that there is some probability of change in blood group of an individual after chemotherapy treatment. An infusion reaction with docetaxel may have altered the expression of blood group antigens in the patient. Anthracycline caused no severe reaction so it can potentially be assumed that it had little to no part in the blood group switch. The causes are unclear. However, a connection between chemotherapy and the change in blood group is possible.

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Conflict of Interest

The authors declare no conflicts of interest.

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