Case report

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Hemolytic reaction due to ABO incompatibility in postpartum transfusion: Case report

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Abstract

ABO group incompatibility at the time of transfusion of blood products carries risks ranging from mild adverse reactions to death of the patient. In modern obstetrics, the leading cause of death is obstetric hemorrhage, for which uterotonics, compression sutures, arterial ligatures, solutions, and blood products are used. For this reason, it is necessary to know the blood group and Rh of each patient admitted for obstetric surgery and have her sign a consent form for transfusion of blood or blood derivatives, explaining all the adverse effects that may occur in the event of complications. We describe a case of postpartum transfusion with a hemolytic reaction due to ABO incompatibility and its clinical management.

Introduction

More than a century after Landsteiner first described the ABO blood group system, it continues to be of great importance in obstetrics because of the large number of obstetric hemorrhages that occur each year during childbirth and cesarean section, requiring transfusion of blood products to prevent maternal mortality. (1,2)

ABO grouping is essential for transfusing blood with a lower rate of adverse reactions that increase morbidity and mortality. An incompatible transfusion, even in small amounts, can be fatal due to the rapid destruction of red blood cells that occurs rapidly at the intravascular level, followed by disseminated intravascular coagulation, renal failure, and ultimately death. (3)

Transfusion with ABO-incompatible blood carries significant risks, and all transfused patients should be closely monitored for the first 30 minutes. During this time, any reaction may require immediate discontinuation of the transfusion. The incompatibility of the ABO group is due to the presence of antigens in the erythrocytes from the fifth week of the embryonic stage, which is fully developed until after birth, since during the infant stage, terminal sugars are added to the oligosaccharide chain of the erythrocyte membrane, generating specific antigens; the average age at which the antigens of

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groups A and B are fully developed is between 2 and 4 years of age and remains so until the end of life. (4)

The sugars that make up the ABO system are found on the outside of the erythrocyte membrane, attached to the ceramide moiety located in the transmembrane portion of the erythrocyte. Attached to this ceramide is a series of 4 sugars, called precursors, to which other sugars are attached to give specificity to each ABO antigen, (5) as shown in **Figure 1**.

The hemolysis process is due to an immunologic response using an antigen-antibody reaction, which in turn activates proinflammatory cytokines and monocytes, producing intravascular fibrin deposits, which activate tissue factor and tissue plasminogen activator (t-PA) inhibition, resulting in disseminated intravascular coagulation and hemolysis. Reactions occurring immediately after transfusion are immunoglobulin (Ig)M-mediated, with intravascular hemolysis predominating, whereas late hemolytic responses are mediated by IgG antibodies, resulting in extravascular hemolysis. (6)

Acute hemolytic reactions (AHR) occur when recipient antibodies interact with incompatible donor red blood cells, activating the classical complement pathway. This results in the destruction of red blood cells, primarily due to ABO incompatibility. IgM antibodies, which can be activated at 37 degrees, are mainly responsible for the lysis of red blood cells, although IgG antibodies may also play a role. The binding of donor red cells with recipient antibodies causes intravascular hemolysis, releasing hemoglobin (Hb) and enzymes into the surrounding tissue. Hemoglobin dissociates rapidly; the heme component is oxidized to methemoglobin, while the globin component binds to haptoglobin in the plasma. The heme oxidation products are bound by hemopexin. Any excess heme that cannot be taken up by hemopexin is bound to albumin, forming methemoglobin. (7)

When the transporter proteins become overwhelmed, hemoglobin is filtered at the glomerular level and can show up in the urine, typically at levels above 150 mg/dl. The complement system also triggers other systems, like the intrinsic coagulation system, leading to fibrin formation. At the same time, releasing intracellular thromboplastin from red blood cells reinforces this process by activating the extrinsic mechanism, causing disseminated intravascular coagulation (DIC). The consumption of various coagulation factors and platelets with fibrin deposits in the capillaries marks this condition. When it affects the renal circulation, it leads to varying degrees of insufficiency based on the damage. Activation of factor XII stimulates the pre-kallikrein activator to convert pre-kallikrein to kallikrein. Enzymatic removal of a terminal peptide then converts kallikrein to bradykinin, which causes arteriolar relaxation, diverting blood from arteries to venous capillaries and significantly reducing mean pressure. Complement fragments (C3a, C5a, and the C5 complex) and various effector cells, including mast cells, can produce additional pharmacological effects, such as releasing vasoactive compounds like serotonin and histamine. In response to stress, variable amounts of catecholamines are also released from the adrenal medulla during the hemolytic response (**Figure 2**). (7)

The true incidence of adverse transfusion reactions has yet to be well known. Still, ABO incompatibility is estimated to be 1 in 38,000 transfusions of erythrocyte concentrates (ECs), with a case fatality rate of 1 in 1,800,000 transfusions and an acute hemolytic reaction rate of 1 in 12,000 transfusions. (8)

Postpartum bleeding following childbirth is not common, happening in just 0.9% to 2.5% of cases. (9) However, the occurrence of postpartum bleeding is increasing worldwide. (10) Most instances of needing a red blood cell transfusion after childbirth are a result of sudden and severe anemia caused by postpartum bleeding, which is essential to identify as it is associated with maternal health problems. (11) Recognizing patients who require transfusion support and ensuring it is sufficient is critical. Prompt diagnosis and treatment can prevent deaths related to postpartum bleeding. (12) There isn't a single, agreed-upon definition of postpartum bleeding. Still, it is frequently defined as losing 500 ml or more of blood within 24 hours of vaginal delivery or over 1000 ml after a cesarean section. Severe postpartum bleeding is characterized by losing 1000 ml or more of blood, and life-threatening massive postpartum bleeding is defined as continual blood loss of over 2500 ml or hypovolemic shock within the same timeframe. (12) Other definitions involve a decrease in hematocrit of over 10% from baseline or a reduction in hemoglobin of 4 g/dl from levels before childbirth. (12) The overall occurrence of postpartum bleeding is approximately 6-11%, and the frequency of severe postpartum bleeding is estimated to be 1-3%, with notable regional differences. (13) Uterine atony is the most frequent cause of postpartum bleeding, with other causes including genital tract trauma, uterine rupture, retained placental tissue, and maternal coagulopathy. (14) Clinical episodes of T-cell beta receptor (tCBR) necessitate special attention as they might be related to severe maternal health issues. (15) Experts in patient safety recommend reviewing the clinical rec-

ords of patients with tCBR to discover areas for enhancement and prevent critical occurrences.
We present the case of a postpartum patient with ABO group incompatibility after a transfusion of blood products. Given the rarity of these cases, their diagnostic difficulty, and the scarcity of reports in the literature, it is essential to communicate them to increase our knowledge.

Ethical issues
No risks have been taken into account, and no fundamental principles have been violated in this research since it has been conducted using existing records and medical records/electronic files. The confidentiality of the information has been maintained. Thus, the researcher was the only one authorized to handle the data obtained exclusively for purposes corresponding to the study under the registration number before the Ethics Committee number 202408-55.

Clinical case
The patient was a 23-year-old woman with a second pregnancy with a gestation of 33.1 weeks, who was referred from the outpatient clinic for presenting elevated blood pressure (144/97 mmHg). On arrival at the clinical, an ultrasound was performed, which reported a single live product, cephalic presentation, with a fetal heart rate of 145 beats per minute, and vaginal examination with dehiscent posterior cervix. Personal pathological history questioned and denied. Obstetric and gynecological history: menarche 13 years, menstrual cycles of 28 by five days, two pregnancies with a history of curettage, six prenatal control consultations, and two normal ultrasound reports. Pathological personal history: questioned and denied; non-pathological personal history: housewife occupation, in free union, incomplete high school, denies drug addiction, chemotype O Rh+, denied transfusions and allergies.
She was admitted to surgery for protocol classification of hypertensive disease to be classified and close follow-up of the binomial. During her stay in the obstetric surgery department, a pre-eclamptic profile, 24-hour urine collection, and antenatal profile were requested, as well as a blood pressure reading of 156/110 mmHg, so the patient was classified as having pre-eclampsia with severity criteria based on blood pressure numbers. She then presented with persistent fetal bradycardia of 50-60 beats per minute, and the decision was made to terminate the pregnancy via the abdominal route. With the operative findings of a single live male product of 2096 grams, size 45 cm, Apgar score 6-8, clear amniotic fluid, euthymic uterine cavity, a 30% premature detachment of normal insertion placenta was reported, with a septate uterus with two cavities. During the operation, she presented uterine atony, and transfusion of 3 erythrocyte concentrates (EC) was indicated because there was no permissible bleeding due to grade III anemia (**Table 1**). During the transoperative period, due to severe anemia, we administered an EC of 254 ml of group O Rh+ factor without complications and adverse reactions and a second EC of 233 ml of group A Rh+ factor without apparent adverse reactions.
During her stay in the surgical recovery room, the elevated blood pressure levels persisted even with a dual antihypertensive regimen based on nifedipine 30 mg orally every 8 hours and telmisartan 80 mg every 12 hours. The pre-eclamptic control profile showed hyperbilirubinemia, elevated liver enzymes, and high-density lipoprotein (HDL) (**Table 1**), so she was referred to the Obstetric Intensive Care Unit (UTIO), which decided to admit her for close follow-up due to suspicion of developing hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome.
On her first day in the UTIO, after reviewing the medical records, HELLP syndrome and pregnancy-related liver disease were ruled out, and a diagnosis of ABO incompatibility was made. On the first day of her stay in the UTIO (**Table 1**), she persisted with grade II anemia, with no clinical data of gastrointestinal discharge, so transfusion of blood products was not considered; a third antihypertensive (metoprolol 100 mg every 12 hours) and steroids (dexamethasone 8 mg IV every 12 hours) were added to the management.
On the second day of hospitalization in the Intensive Care Unit (ICU), the patient was asymptomatic, with blood pressure within the target range (116/80 mmHg). Treatment continued with enoxaparin 40 mg subcutaneously every 24 hours, urine without macroscopic appearance of hematuria (Vogel II), with urine output of 3.76 ml/kg/hour spontaneously, with persistent anemia, and a decrease in total bilirubin and HDL (**Table 1**). So, it was decided to discharge her from the ICU on the third day of admission to continue her stay in the obstetrics ward with control laboratories.
On her first day in the obstetric ward, the patient was stable, with blood pressure within target parameters, biochemically with grade III anemia, bilirubin within normal parameters, and HDL continuing to decrease, so her discharge was evaluated with control laboratories.
The patient was discharged after a two-day stay in the obstetric ward with a diagnosis of pre-eclampsia with severity criteria based on blood pressure, sur-

gically induced pathologic puerperium, grade III anemia, hepatic dysfunction in remission due to ABO incompatibility, with antihypertensive management with a triple regimen based on long-acting calcium channel blockers and angiotensin II receptor antagonists, beta-blockers and angiotensin II receptor antagonists, oral anticoagulants, analgesics, and antibiotics, with an open appointment to the emergency department in case of alarm data.

Discussion

The treatment of obstetric hemorrhage, in addition to uterotonics, compression sutures, and ligation of the uterine and hypogastric arteries, is supplemented by transfusion of blood products. The latter is considered a procedure whose therapeutic purpose is to correct the hematologic deficit, which, although considered safe and effective, is not free of complications since mild and severe adverse reactions may occur, ranging from rash to death. (16) Complications can also be classified according to the presentation time as acute, occurring within the first 24 hours after transfusion of a blood product, and late, occurring after the day of the procedure, which should be recognized, managed, and reported by trained personnel. (17)

Transfusion-associated hemolysis is a true emergency because it is life-threatening and occurs as a result of an immune system reaction due to a mismatch between red cell membrane agents and specific antibodies present in the plasma. This reaction can be accompanied by the sudden onset of dyspnea, nausea, back pain, and flushing, as well as hemoglobinuria, fever, disseminated intravascular coagulation, and renal failure (8,18). In our case, the patient presented with symptoms of hemodynamic instability plus hemoglobinuria, initially thought to be hematuria.

It is essential to make a differential diagnosis before initiating treatment since some pathological entities that occur during pregnancy may be similar, such as hemolytic anemia induced by drugs, especially antibiotics; within these, in obstetrics, we use cephalosporins as prophylaxis before surgery, as well as non-steroidal anti-inflammatory drugs also related to this pathology, IgG mediates the hemolytic reaction in this case and produces severe hemolysis. (19,20) In this case, drug-induced hemolysis was excluded due to the group of blood products transfused to the patient. However, we must keep in mind that other diagnoses must be ruled out during pregnancy, such as HELLP syndrome, thrombocytopenic purpura, and hemolytic uremic syndrome. (20) These were ruled out in the patient.

Human error is a cause of adverse ABO reactions due to the timing of blood collection for crossmatching at the blood bank or during the administration of blood products. It is essential to know the compatibility of the different blood groups to identify donors and recipients based on Rh and ABO groups, thus reducing the likelihood of an incompatibility reaction (**Table 2**). (8) In our case, two chain errors occurred because the EC transfused to the patient was not truthfully confirmed by the staff in charge of the blood bank and the surgical recovery area.

Treatment of acute hemolytic transfusion reaction is based on immediate discontinuation of the transfusion and prompt communication with the blood bank, which should objectively review records for mislabeled blood product packages and notify emergency or critical care physicians to initiate timely treatment. (21) Medical management after transfusion cessation is based on the administration of intravenous solutions to restore blood pressure and normal diuresis; urine should be alkalinized by administering an ampoule of bicarbonate in Ringer's lactate solution; and direct and indirect Coombs tests, blood biometry, blood urea nitrogen, and a urine sample should be obtained to quantify urinary hemoglobin. (22)

Conclusion

ABO-related adverse reactions after blood product transfusion are infrequent and potentially life-threatening. A specialized medical team should treat the suspicion and identification of an adverse reaction as a true emergency, and the blood bank should be notified for confirmation of data and blood compatibility. Human error is a reality that can be prevented by maintaining appropriate controls in the blood product administration chain.

Table 1. Laboratory results

	Admission delivery room 14/02/2024 16:12 hrs	Postpartum results 15/02/2024 02:32 hrs	ICU			Obstetrics area	
			Day 1 15/02/2024 05:26 hrs	Day 2 16/02/2024 05:36 hrs	Day 3 17/02/2024 06:45 hrs	Day 1 18/02/2024 06:40 hrs	Day 2 19/02/2024 07:11 hrs
Hb, g/dl	6.5	8.4	7.8	7	7.1	7	7.3
Hematocrit, vol %	24.9	29.6	28.7	26.2	26.3	26.5	28.0
WBC, $x10^9$/l	2.88	3.40	2.99	3.90	4.39	4.12	4.36
Platelets, $x10^9$/l	91	246	242	313	283	151	116
PT, sec	14.1	-	15	14.3	-	-	-
PTT, sec	38.2	-	33.9	35.1	-	-	-
Glucose, mg/dl	80.7	107.6	110.2	84.2	60.7	60.6	65.5
Urea, mg/dl	5.8	9.6	12.8	12.2	19.9	16.2	14.1
BUN, mg/dl	2.7	4.4	5.9	5.7	9.2	7.5	6.5
Creatinine, mg/dl	0.34	0.47	0.44	0.39	0.37	0.32	0.26
TB, mg/dl	0.3	2.2	3.5	0.87	0.4	0.4	0.4
DB, mg/dl	0.22	0.16	0.64	0.43	0.27	0.25	0.24
IB, mg/dl	0.14	2.03	2.8	0.40	0.21	0.19	0.23
ALT, IU/l	10.8	69.3	65	25.9	13.2	12.6	10.4
AST, IU/l	5.9	10.9	10.4	12.2	10.8	12.6	11.3
Albumin, mg/dl	3.5	-	3.2	3.5	-	3.3	-
LDH, IU/l	197	1701	1598	960	597	443	393
ALP, IU/l	141	164	133	133	121	118	121
K, mEq/l	-	3	-	2.65	2.87	3.4	3.36
Na, mEq/l	-	141.1	-	143	144	140	141
Ca, mg/l	-	8.1	8.2	8.2	8.2	8.3	8.5
PO4, mg/dl	-	3.4	1.1	5.43	3.9	4.8	4.9
Mg, mg/dl	-	2.6	3.1	2.64	2.12	2.24	1.7
Cl, mEq/l	-	113.8	-	106.5	106.9	106.6	105

Legend: ICU=Intensive Care Unit; Hb=hemoglobin; WBC=white blood cells; PT=prothrombin time; PTT=partial thromboplastin time; BUN=blood urea nitrogen; TB=total bilirubin; DB=direct bilirubin; IB=indirect bilirubin; ALT=alanine aminotransferase; AST=aspartate aminotransferase; LDH=lactic dehydrogenase; ALP=alkaline phosphatase; K=potassium; Na=sodium; Ca=calcium; PO4=phosphorus; Mg=magnesium; Cl=chloride.

Table 2. Blood compatibility (taken from A. Gutiérrez-Martín et al.)

Blood type	Can donate to	Can receive from
O+	A+, B+, AB+, O+	O+, O-
O-	A+, A-, B+, B-, AB+, AB-, O+, O-	O-
A+	A+, AB+	A+, A-, O+, O-
A-	A+, A-, AB+, AB-	A-, O-
B+	B+, AB+	B+, B-, O+, O-
B-	B+, B-, AB+, AB-	B-, O-
AB+	AB+	A+, A-, B+, B-, AB+, AB-, O+, O-
AB-	AB+, AB-	A-, B-, AB-, O-

Figure 1. Structure of the antigens of the ABO system (taken from A. Gutiérrez-Martín et al.)

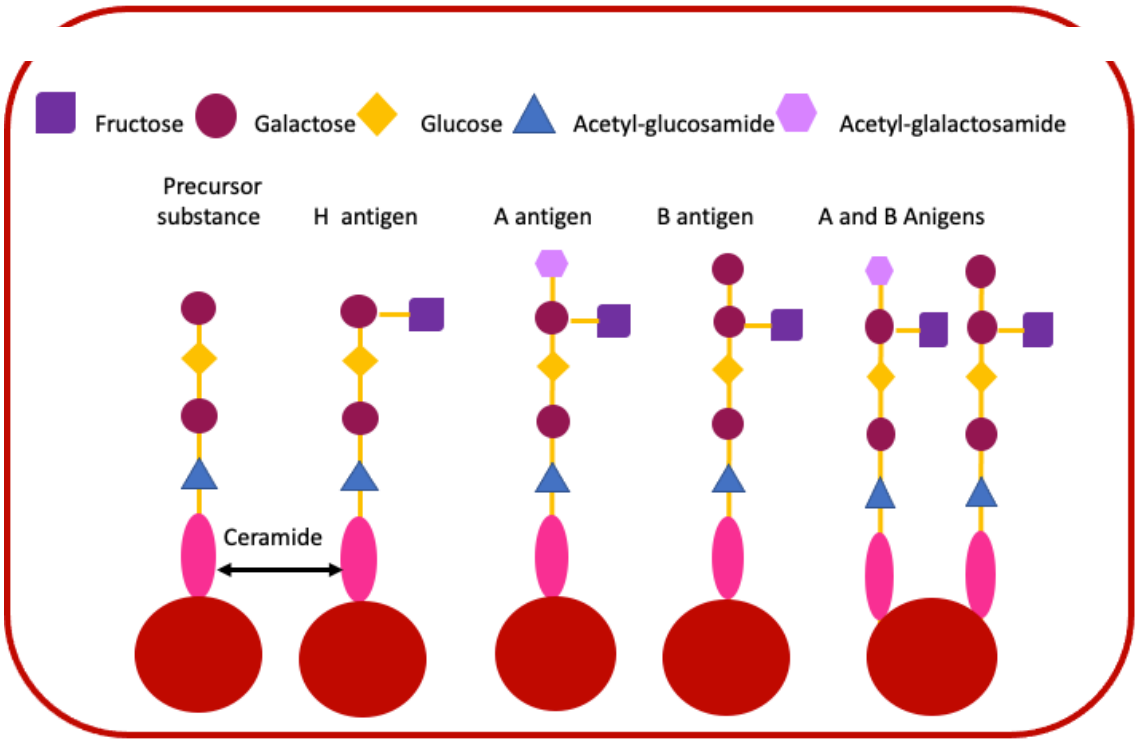
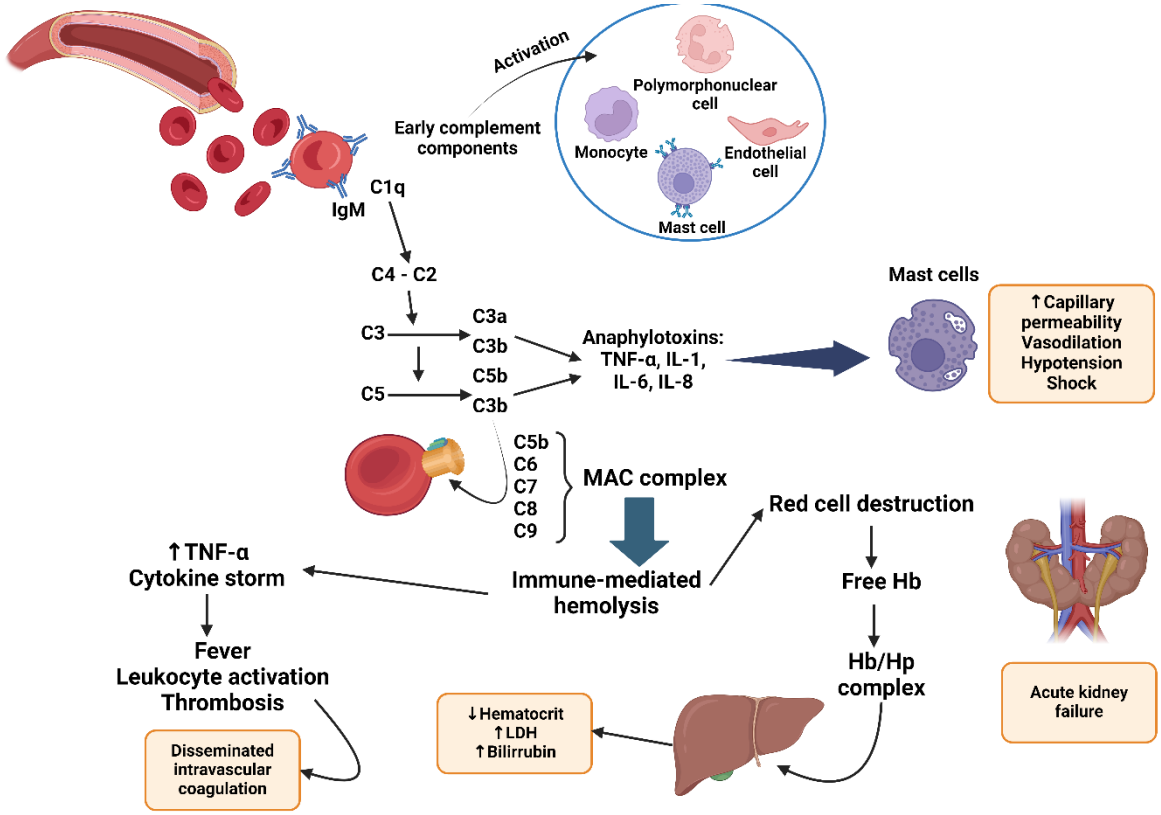


Figure 2. Understanding the pathophysiology of acute intravascular hemolysis



Legend: C=complement; IgM=immunoglobulin M; TNF-α=tumor necrosis factor alpha; IL=interleukin; MAC=membrane attack complex; Hb=hemoglobin; Hp=haptoglobin; LDH=lactate dehydrogenase.
IgM molecules play a pivotal role by efficiently binding and activating complement within the intravascular space, subsequently destroying immune-mediated intravascular cells.

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