Case Report

Delayed Hemolytic Transfusion Reaction due to Anti-Jk^b: Case Report Highlighting the Importance of Early Blood Bank Consultation and Literature Review

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Abstract

Delayed hemolytic transfusion reactions (DHTR) can be asymptomatic or mimic other conditions and may be misdiagnosed. Failure to recognize this entity could lead to inappropriate treatment and future transfusions reactions. Anti-JK^a and anti-JK^b are the most frequently encountered antibodies responsible for DHTR ac companied by intravascular hemolysis on rare occasions. The antibodies are often difficult to detect because of their transient nature and their frequent dosage effect. We report the case of a 40-year-old female with DHTR due to unexpected weakly reactive anti-JK^b. The patient, with a medical history of hypertension, multiple transfusions, multiple abortions and vaginal bleeding due to uterine fibroids, presented to our emergency department complaining of back pain for four days and red-brown color urine for one day. Significant jaundice was noted on physical examination. Laboratory data showed low hemoglobin (Hb) (6.0g/dl) and increased creatinine (3.11 mg/dl). Differential diagnosis included hemolytic-uremic syndrome, hematuria caused by urinary tract calculi, and autoimmne hemolytic anemia. Significant hemolysis was observed in the patient's blood sample. Further questioning elicited a recent blood transfusion seven days prior. Red cell antibody work-up at that time showed the presence of anti-K and anti-E. The patient was transfused 2 units of K and E antigen negative cross-match compatible packed red blood cells(PRBCs). Post-transfusion Hb was 8.8 g/dl and there were no signs of any immediate complication. Review of the recent history of blood transfusion and the current findings led to our strong suspicion of intravascular hemolysis. The patient was treated vigorously with fluids and intravenous diuretics. Stat tests subsequently confirmed the intravascular hemolysis. A 'new' request for blood transfusion was put on hold while an antibody workup was initiated. Red cell antibody work-up results confirmed the presence of anti-K and anti-E; the direct antiglobulin test (DAT) was negative. An eluate prepared from the patient's red cells was non-reactive by indirect antiglobulin test. Additional samples were sent to a reference laboratory for further investigation of unexpected red cell antibodies. Results from the reference laboratory confirmed the anti-E and -K, and, in addition, a weak anti- JK^b was identified in the plasma and eluate. Both of the prior transfused units were subsequently shown to be Jk(b+), adding further evidence that the anti-JK^b is most likely the culprit of the DHTR. The patient was subsequently transfused with E-, K- and Jk(b-) PRBCs and her condition improved. This case emphasizes the central role of blood bank consultation for early treatment and diagnosis of DHTR and for the avoidance of incompatible blood component transfusion, thus minimizing the risks of morbidity and reduce the potential for mortality. It is our opinion that blood bankers should be consulted when patients have an acute drop in Hb following recent transfusions. Moreover, transfusion medicine should be part of medical school education and part of hospital grand round conferences, to raise clinicians' awareness to improve recognition and reporting of DHTR so that timely diagnosis and treatment can be made.

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Introduction

Blood transfusions are a common therapeutic modality in all areas of medicine. Known transfusion complications include hemolytic transfusion reaction (HTR), infections, transfusion

associated acute lung injury, allergic reactions, volume overload, iron overload, and febrile/immunological reaction, etc. Modern blood banking and therapeutic interventions have ameliorated the frequency and/or severity of these complications.[1]

Many physicians are familiar with the typical acute blood transfusion reactions (AHTR), which occur during the transfusion or within 24 hours after the transfusion. Any transfusion reaction occurring beyond 24 hours after blood transfusion is arbitrarily defined as a delayed transfusion reaction.[2]

HTR usually results from recipient plasma alloantibodies (i.e. antibody against a foreign antigen) to donor RBC antigens. Immunohematology studies for HTR usually reveal a positive DAT and the implicated alloantibody in elute. The same antibody is usually found in the serum/plasma.[2]

HTR may be acute (within 24 h) or delayed (from 1 to 16 days). Either AHTR or delayed HTR (DHTR) may be associated with intravascular hemolysis or extravascular hemolysis.[2]

If the red blood cell (RBC) antibody is capable of complement binding, the interaction of antibody with antigen on the red cell membrane can initiate a sequence of complement activation, which leads to the development of the membrane attack complex, causing lysis of RBCs, i.e. causing an intravascular hemolysis. Acute renal failure, shock and/or disseminated intravascular coagulation (DIC) are the potential fatal complications of intravascular hemolysis due to cytokine and coagulation effects, and other elements of a systemic inflammatory response. Diagnosis of intravascular hemolysis is confirmed by free hemoglobin (Hb) in the plasma and urine (hemoglobinemia and hemoglobinuria), a fall in Hb/ Hct, elevated serum LDH, and a very low haptoglobin level; hyperbilirubinemia may follow.[2]

If the RBC antibody does not activate complements, the RBCs coated with antibodies are phagocytized by liver and spleen resident-macrophages, resulting in extravascular hemolysis. The engulfed hemoglobin converts into iron for recycling and the globin portion becomes bilirubin later. Since the RBCs are not lysed in the circulation, LDH is not elevated. Additionally, hemoglobin is not released into the circulation so haptoglobin is not consumed and hemoglobinemia/ hemoglobinuria are not observed. Since portions of RBC membranes are engulfed by the phagocytes, microspherocytes can be seen in the peripheral blood smear. Extravascular hemolysis is usually slow and the clinical manifestations are mild, with a slow rise in bilirubin level. Unlike intravascular hemolysis, in general there is no fatal complication in association with extravascular hemolysis.[2]

The most severe HTRs usually occur acutely when transfused RBCs interact with preformed antibodies in the recipient. AHTR is among the most severe transfusion reactions. ABO incompatibility is the most common cause of AHTR, which causes a high rate of mortality and morbidity. Although antibodies against blood group antigens other than ABO can also cause AHTR. Mislabeling the recipient's pretransfusion sample at collection or failing to match the intended recipient with the blood product immediately before transfusion is the usual cause of AHTR.[2]

ABO antibodies, anti-A, anti-B and anti-A,B, are so called "naturally occurring" antibodies. Ordinarily individuals possess antibodies directed toward A or B antigen absent from their own red cells. These antibodies usually develop after first few months of life, and the production increases to adult level at 5-10 years of age. Anti-A, anti-B and anti-A,B are predominantly IgM, which are capable of complement binding and activation.[3,4]

Antibodies against blood group antigens other than ABO can cause AHTR or DHTR. The non-ABO IgG alloantibodies most commonly arise from sensitization to foreign red blood cell antigens during pregnancy or transfusion, or less commonly during transplantation.[3,5,6]

Early recognition of symptoms suggestive of a HTR and prompt reporting to the blood bank are essential. During or within 24 hours after transfusion, fever, chills, hemoglobinuria, back pain, flank pain, hypotension, renal failure, and/or DIC (oozing at IV site, diffuse bleeding at surgical site, abnormal DIC test results) usually trigger a prompt report, diagnosis and treatment for an AHTR.[2]

Delayed hemolytic transfusion reaction (DHTR), however, occurs 24 hours post-transfusion, usually 5-7 days (can be 4 - 16 days, or up to 4 weeks) after transfusion. Due to its latency, DHTR is not well recognized, resulting in significant morbidity and mortality if not managed promptly.[2,7,8] DHTR may also occur within a few hours after transfusion, due to an anamnestic antibody response from re-exposure to foreign RBC antigen.[2] Blood bank serological finding include a positive direct antiglobulin test (DAT) (IgG and/or C3), and a new antibody in the eluate and serum/plasma. The implicated antibody is often not detectable in the patient's pre-transfusion specimens due to very low concentration, but quickly become detectable in the post-transfusion specimen, supporting the anamnestic antibody response. In most cases, anamnestic antibody production does not cause hemolysis, leading to the designation "delayed serologic transfusion reaction (DSTR)".[2,9] In DSTR, there are positive serological findings, but the patient is asymptomatic and clinical signs are absent. On the other hand, DHTR occurs when the antibody develops rapidly in primary or anamnestic response to antigens on transfused red cells. The newly forming antibody destroys the still circulating transfused red cells. One clinical clue for DHTR may be an unexplained drop in Hb/ Hct to the pretransfusion level occurring 1 to 2 wk posttransfusion. Rarely, severe symptoms occur, resulting in a falling Hb/Hct and a rise in LDH and bilirubin. Severe DHTR only rarely happen when the red cell destruction result from the combination of significant levels of antibody with hemolytic potential and large numbers of transfused red cells in the circulation.[2]

Anti- Jk^b and anti-Jk^a, the antibodies in Kidd blood group, are generally found in antibody mixtures. They are notorious as they may cause severe AHTR and DHTR. They are predominantly IgG1 and IgG3. The hemolytic potential of these unusual IgG antibodies is due to the fact that 50% of anti- Jk^b and anti-Jk^a bind complement, which subsequently activate the complement to cause intravascular hemolysis. Kidd antibodies are a common cause of DHTR, probably because they are often not detected in pretransfusion testing. The antibodies are often hard to detect and identify because they are usually weakly reactive, with low titers, and are detected primarily at the antiglobulin phase of testing. These antibodies often show dosage, meaning that a Kidd antibody sometimes may be detectable only with the reagent cells bearing homozygous Kidd antigen.[3,5] The antibodies have a tendency to rapidly drop to low levels in the circulation and also in stored serum/plasma, typically falling below levels detectable by routine blood bank serologic methods. This is why Kidd System antibodies are commonly referred to as "transient in nature". However, the existence of their memory lymphocytes enables Kidd antibody to dangerously mount a brisk anamnestic response when exposed to the Kidd antigen on transfused RBCs. Because of Kidd antibody's common involvement in DHTR and intravascular hemolysis, and the difficulty of antibody detection, early consultation with blood bank/transfusion service is recommended for any suspected DHTR case.

We report a case of anti-Jk^b induced DHTR, which highlights the importance of early consultation of the blood bank and education of clinicians for DHTR. A review of the literature is also included.

Case Report

A 40-year-old Jamaican woman with history of hypertension, multiple abortions and uterine fibroids with vaginal bleeding, presented to our emergency department (ED) complaining of progressive flank pain for 4 days, nausea and red colored urine for 1 day. The patient also had complaints of shortness of breath (SOB) on exertion, fatigue, and light-headedness for recent 2-3 days. She denied having chest pain or orthopnea. On examination, she was tachycardic and her temperature was 101°F; her blood pressure was within normal limits. Significant findings included scleral icterus and pale frenulum; hepatosplenomegaly or costovertebral angle tenderness was absent. Vaginal bleeding was noted on the pelvic exam. The patient was able to produce urine in the ED, which was red-brown colored. She had no prior history of red urine. Urine output was not measured in the ED. Laboratory data showed decreased hemoglobin (Hb) (6.0 g/dl) and increased creatinine (3.11 mg/dl) (**Table 1**: Day 0). Nephrology consult was attained and a renal CT was ordered for renal disease work-up. The peripheral blood smear showed slight microcytosis and moderate hypochromia. No schistocytosis was seen and the platelet count was within the normal range. Computer tomographic (CT) scanning of abdomen and pelvis showed 0.5cm non-obstructing right-sided renal calculi with trace amount of blood in the uterine cavity. In summary, the patient presented with a low-grade fever, red colored urine, jaundice, symptomatic anemia, marked acute renal failure, and vaginal bleeding with CT scan evidence of nephrolithiasis.

Table 1. Selective Laboratory Data of the Patient.

Laboratory Test	**6 months previously**	**Day -7**	**Day -5**	**On admission (Day 0)***	**Day+1**	**Day +2**	**Day +3**
Antibody Screen	Negative	Positive		Positive**			Positive
Antibody identification (in patient's serum/ plasma)		Anti-E, -K		Anti-E, Anti-K, Anti -Jk^b**			Anti-E,-K
DAT		Negative		Negative**			Negative
Eluate		Negative		Anti-Jk^b**			Negative
Units of RBC Transfusion	2	2		2			
Hemoglobin (g/dL)	6.6	6.2	8.8	6.0	8.7	8.3	8.3
Lactate Dehydrogenase (LDH)				2461		2211	
Billirubin Total/ Indirect (mg/ dL)		0.1/ ND		1.6/1.5		0.24/ ND	
Haptoglobin (mg/ dL)				<20		<20	
Creatinine (mg/ dL)	0.85	0.96		3.11	3.49	3.71	3.39

Note:
*: Specimens were grossly hemolyzed.
**: The test was performed by both the reference laboratory and the hospital blood bank.
ND: not determined.

The working diagnosis in the ED was hemolytic-uremic syndrome (HUS). Renal calculi and autoimmune hemolytic anemia were included in the differential diagnoses. Hematology consult was requested given the picture of hemolysis. Two units of packed red blood cells (PRBC) were requested by the ED physician to treat the patient's symptomatic anemia.

Gross hemolysis in the blood sample sent to the blood bank alerted the blood bank medical director (BB director henceforward in this manuscript) to suspect a DHTR and immediately saw the patient. The BB director elicited a transfusion history from the patient and further collateral information was obtained from an outside hospital where the patient had been recently transfused. The patient was diagnosed with iron deficiency anemia secondary to menorrhagia, found to be blood type O, Rh positive and was given 2 units of PRBC about 6 months previous to her current presentation at ED. Her pre-transfusion antibody screen was negative (**Table 1**: 6 months previously). She was discharged with iron supplementation. Seven days before the current presentation, she presented to another outside hospital with complaints of dyspnea and fatigue. Hemoglobin (Hb) was found to be 6.2g/dL. Anti-E and anti-K red cell alloantibodies were detected in the plasma/serum, and a direct antihuman globulin test (DAT) was negative (**Table 1**: Day -7). The patient was transfused with 2 units of E and K antigen negative, cross-match compatible PRBCs, and discharged with a post-transfusion Hb 8.8g/dl. When the patient presented to the ED this time (**Table 1**: Day 0), her Hb was found to be near the pre-transfusion level, suggesting hemolysis of virtually all, or most, of the transfused red cells.

With a high index of suspicion for DHTR, the BB director immediately started a stat antibody workup as well as working in collaboration with the ED clinicians for treatment of DHTR. To avoid giving potentially incompatible blood products (i.e. implicated antigen positive blood) to the patient, which would worsen the patient's hemolysis, a hold was placed on the blood request until antibody studies were completed.

The BB director explained to the ED treating physician and housestaff the dangers of intravascular hemolysis and the associated potential fatal complications, the high probability of DHTR in this case, and the rationale to temporarily hold the blood request. The BB director also told the ED clinicians, that in case the patient developed hemodynamic instability before the cause of the hemolysis was found by the antibody workup, E(-) K(-) crossmatch compatible PRBCs would be given to the patient as emergency release. Upon the BB director's request, the patient was started on vigorous fluids and intravenous diuretics to keep the patient's urine output more than 70ml/hour. The patient's vital signs were closely monitored, and stat tests for urinalysis, LDH, PT/ PTT, haptoglobin ordered. The diagnosis of hemoglobinuria was inconclusive because urinalysis showed numerous RBCs. However, markedly increased LDH and decreased haptoglobin indicated an intravascular hemolysis. The patient was admitted to a medical unit on Day 0.

The hospital blood bank performed an antibody workup for the patient's specimen using manual tube technique. The DAT was performed by using polyspecific anti-human globulin (AHG), anti-IgG and anti-C3. Although the DAT results were negative, a rapid acid elution was performed, because it is a more sensitive test, in order to detect the antibody coating the patient's red blood cells. Indirect antiglobulin test (IAT) with polyethylene glycol (PEG) as the potentiating agent was used to identify antibody in the plasma. Anti-K and anti-E were identified in the plasma, but no antibody was detected in the eluate. Anti-K and anti-E are the pre-existing antibodies, but no antibody was identified as the culprit of the current intravascular hemolysis.

The BB director was not convinced with these findings and decided to send the patient specimen stat to an immunohematology reference laboratory. The reference laboratory performed antibody workup using basically the same methodologies as did the hospital blood bank. However, a weakly reactive anti-Jk^b was identified in both the eluate and plasma. In addition, the reference laboratory studies confirmed previous identified anti-E and anti-K in plasma.

The patient was then administered Jk(b-), K(-) and E(-) blood. The patient's clinical condition was partially improved as red urine and back pain subsided, and she felt better on Day 3 after the admission, although her renal function (BUN/creatinine level) was not significantly improved at that time.

The antibody workup was repeated at the hospital blood bank by 3 more technologists; only one out of these three technologists detected the weak anti- Jk^b in plasma and eluate.

Further studies by the outside hospital blood bank were conducted and revealed that both units transfused 7 days prior were phenotyped Jk(b+) positive, supporting that the anti-Jkb was the culprit of the DHTR.

The patient signed out against medical advice 3 days after admission, but she was given a letter documenting the presence of E, K, and -Jk^b red-cell alloantibodies by the BB director, to be used as an 'alert' for future transfusions.

Discussion

Delayed hemolytic transfusion reaction (DHTR) is a process that occurs 24 hours post-transfusion. DHTRs are relatively common following blood transfusions, and represent approximately 11% of all complications of RBC transfusions.[2,10] The mechanism is due to allo-antibodies formed against foreign RBC antigens (e.g., Rh, Kell and Kidd antigens).[2,11] The Kidd blood group system antigens (Jk^a, Jk^b, and Jk^3) was first described in 1951[12] and are estimated to be responsible for more than a third of all DHTRs.[9]

The prevalence is probably underrepresented due to the transient and weakly reactive nature of the antibodies and the

difficulty of *in vitro* detection.[3,5] Generally, they are detected at the antiglobulin phase of testing. Therefore, Kidd antibody-induced DHTR represents a diagnostic challenge for internists. Antibodies in the Kidd blood group system notoriously cause intravascular hemolysis, which have the potential for fatal complications, such as acute renal failure, shock, and DIC. It is important for clinicians to have a high index of suspicion for Kidd antibody induced DHTR, especially where there is a history of recent transfusion. However, clinicians may not recognize DHTR due to its latency, so that the history of transfusion, pregnancy and history of RBC antibodies are important elements in the history inquiry. As noted before, Kidd antibodies may go undetected due to its transient nature because of its propensity to rapidly fall below the levels of routine blood bank serologic testing; therefore, these antibodies (anti-Jk^a or anti-Jk^b) induced DHTR may go unrecognized, resulting in inappropriate diagnosis and management. Its ability to mount a brisk anamnestic response and unusual ability (for an IgG class antibody) to fix complement can lead to significant morbidity and mortality disseminated intravascular coagulation.[13]

In this case report, initially there was a discrepancy of anti-Jk^b detection between the reference laboratory and the hospital blood bank, despite the same methods being utilized. The detection discrepancy also appeared among different technologists in the same hospital blood bank under the same testing conditions. According to a discussion with the technical director of the reference laboratory regarding this discrepancy, the new antibody anti-Jk^b appeared to be very loosely associated with the RBCs, and the antibody-antigen reactive agglutination could be easily dispersed when the test tubes were manually agitated a little bit stronger. Thus the anti-Jk^b could be easily missed due to variation in techniques of shaking tubes during the manually performed testing. It again highlights the difficulty in detection of Kidd antibody.

The finding of a new alloantibody in the eluate of a recently transfused patient with clinical signs and/ or symptoms of hemolysis is diagnostic of DHTR.[14] Other helpful considerations include hemolytic markers, history of transfusions, transplantations, and pregnancies. Hemolytic anemias with similar clinical presentations may also be seen in sickle cell disease, autoimmune hemolytic anemia, glucose-6-phosphate dehydrogenase deficiency, medications therapy (e.g. penicillin and sulfa-drugs) and should be considered in the differential diagnosis.

DHTR is self-limited but can have significant complications such as shock, renal failure, and DIC,[2,15,16] which generally result form intravascular hemolysis. Aggressive hydration combined with intravenous diuretics and avoidance of further transfusion of the offending antigen-positive RBCs will minimize nephrotoxicity secondary to RBC breakdown. The infusion of normal saline combined with use of lasix increases the urine output and ensures adequate renal blood flow, with a goal of urine flow rate > 1ml/ kg/ hour for severe HTR with acute renal failure. The urine output must be carefully monitored so as not to cause volume overload in the patient. If urine output remains diminished after a liter of normal saline infused, acute tubular necrosis and/or pulmonary edema may follow. Stat nephrologist consultation should be attained. Oliguric renal failure may be complicated by hyperkalemia and subsequent cardiac arrest. Metabolic acidosis and uremia often necessitates dialysis.[2]

Low-dose dopamine hydrochloric acid (1-5 ug/ kg/ minute) is generally accepted to be the choice of pressors for hypotension/shock associated with severe HTR. Low-dose dopamine should be considered when an inotropic cardiac effect with renal vasodilation is desired to selectively improve renal blood flow.[2]

DIC may present as oozing at IV site, diffuse bleeding at surgical site. Lab values are consistent with consumption of RBCs (drop in Hb/ Hct) and platelets (thrombocytopenia), consumption of coagulation factors (prolonged PT/ PTT, decreased level of fibrinogen, elevated level of D-Dimer, etc). DIC is extremely difficult to treat. Traditional therapy for DIC includes treating or removing the underlying cause, and providing blood components, including PRBC, Platelets, FFP and cryoprecipitated antihemophlic factor (Cryo AHF).

In sickle cell disease (SCD), DHTR is often a life-threatening transfusion complication including hyperhemolysis syndrome. Hyperhemolysis syndrome is characterized by a marked drop in Hb with destruction of both transfused and autologous RBCs and exacerbation of SCD symptoms. Rituximab (anti-CD20 antibody) has been successfully used for prevention of DHTR in sickle cell populations.[17] Other treatment options include IVIG, corticosteroids[18] or various immunosuppressive medications[19] for suppression of RBC antibody production have all been reported in the literature but the effectiveness of these treatments need further validation and evaluation. Supportive treatments are needed for the complications of DHTR, such as pressors for shock, and/or hemostatic blood components (PRBC, platelets, plasma, Cryo AHF) for DIC.

Prevention strategies for hemolytic transfusion reaction (HTR) include providing the patient with antibody profile card (and/or putting the information on a Medic Alert bracelet), maintaining good hospital records, and minimizing unnecessary blood transfusion.

We reviewed cases of anti-Jk^a or anti-Jk^b triggered DHTR reported in the English literature (Search PubMed on 6/12/2010 for anti-Jk and delayed hemolytic transfusion reaction). The references of each paper were reviewed and only those fitting the criteria for anti-Jk^a or anti-Jk^b induced DHTR were included along with the patient and hemolytic characteristics (**Table 2**). In summary, transfusions ranged between 3 and 15 units with hemolysis occurring between 4 to 16 days post-transfusion. The duration of the hemolysis, if mentioned in the case reports, is between 4-13 days. Anti-Jk^a and anti-Jk^b were predominantly found in patients tested within 3 months post-transfusion.[20]

Table 2. Review of Literature.[21-30]

References	Patient characteristics		Hemolysis Characteristics				
	Age (years old)	Sex	Units transfused prior to DHTR	Starting date (Date post-Tx)	Duration (Days)	Antibody implicated	Treatment
Hareuveni M, et al. Transfusion. 2002;42(3):363-367.	43	male	*	10	*	Anti- Jk^a	steroid, tacrolimus, etc.
Holland PV, et al. JAMA. 1968;204:1007-1008.	50	male	4	13	10	Anti-Jk^b	supportive
Hussain SS, et al, Transfus Med 2007; 17(3):197-199.	66	male	3	11	6	Anti- Jk^b	Steroids
Jamiesson AL, et al. Am J Med Technol 1965; 31(6):297-401.	39	female	7	6	6	Anti- Jk^b	supportive
Kurtides, Salkin MS, Widen AL ES. JAMA. 1966, 197(10):816-817.	58	male	8	8	4	Anti- Jk^b	supportive
Morgan P, et al. Transfusion. 1967; 7(4): 307-308.	36	female	13	4	13	Anti- Jk^b	supportive
Scudder J, et al. J Natl Med Assoc 1960; 52:75-80.	38	Female	**	4	**	Anti- Jk^b	supportive
Shahian DM, et al. Panminerva Med. 1995;37(2):95-97.	74	female	15	14	7	Anti- Jk^b	supportive
Takeuchi K, et al. Thorac Cardiovasc Surg. 1993;41(2):104-106.	42	female	7	14	12	Anti- Jk^b	supportive
Yasuda H, et al. Transfus Sci. 2000; 23(2):107-112.	71	male	14	16	7	Anti- Jk^a	supportive

* Hemolysis gradually subsided, but its duration was not mentioned in the case report. DAT was weakly positive even 6 months post transfusion.
** The number of transfused units and duration of hemolysis were not mentioned in the case report.

The Kidd antibodies rapidly became undetectable within 4 weeks post-transfusion, much sooner than other red cell antibodies.[21] Treatment was mainly supportive, except one case in which the use of steroids was listed; this case had the lowest number of transfusions and the second shortest duration of hemolysis.[23]

Our case illustrates the importance of taking a complete history. Initially, the transfusion history was not elicited, therefore, transfusion-associated complications were not considered. The lack of history, combined with inconclusive laboratory studies, led to a clinically sound, however, misleading working diagnosis of hemolytic-uremic syndrome. It might have resulted in inappropriate management of the patient, if DHTR was not suspected. The turning point of the case was eliciting the transfusion history from the patient, which allowed for a unified mechanism of the underlying pathogenesis. Inquiry of transfusion and RBC antibody history is an often overlooked clinical aspect in ED, but is well recognized by blood bankers as very important and necessary information for a successful transfusion outcome. The DHTR caused lysis of all previously transfused RBCs, explaining the negative DAT (**Table 1**) and the grossly hemolyzed blood samples (**Figure 1**). The identification of the antibody was crucial to the case because it avoided another incompatible transfusion and the potential for further morbidity due to anti-Jk^b induced HTR and allowed for the release of the appropriate PRBC for transfusion.

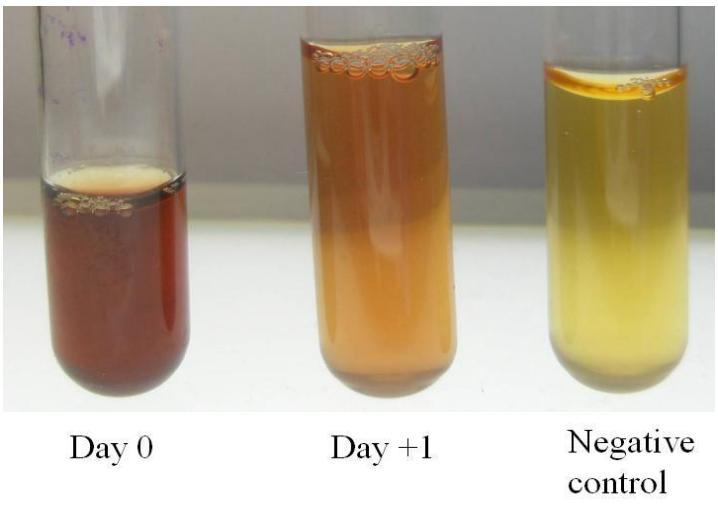

Figure 1. The Patient's Plasma During Hospitalization.
Day 0: the patient's plasma on the date of admission. The plasma revealed a gross hemolysis.
Day +1: The patient's plasma on the day after admission. The concentration of hemoglobinemia appeared less than the one on Day 0.
Negative control: plasma control which is negative for hemoglobinemia.

The patient clinically felt better after receiving fluids and two units of compatible PRBCs (negative for E, K and Jk(b+) antigens). The patient left the hospital prematurely on day 3, with a transfusion letter to alert prospective caring physician to her antibody history, in case she seeks urgent medical attention elsewhere.

Table 3. Signs and Symptoms of Delayed Hemolytic Transfusion Reaction.

Timeline	> 24 hours post transfusion (post-Tx), usually occurs 4-16 days post-Tx, can be more than 16 days (up to 4 weeks).
Symptoms and Signs	fever, back pain, abdominal pain, hemoglobinemia, jaundice, malaise, oliguria, bleeding (oozing).
Laboratory Values	decrease serum hemoglobin, hemoglobinemia, hemoglobinuria, increase lactose dehydrogenase (LDH), decrease haptoglobin, increase indirect bilirubin, increase creatinine, positive urinary hemosiderin; DIC syndrome, positive antibody screen test, positive DAT, new identified antibody in eluate and plasma/ serum.

Although anti-Jk^b implicated DHTR is relatively uncommon, we cannot disregard the possibility of its occurrence and the associated potential for a fatal outcome. See **Table 3** for the clinical signs and symptoms of DHTR. This case also emphasizes the critical role of blood bank consultation for early treatment and diagnosis of DHTR, and for avoidance of wrong blood component transfusion, thus minimizing the morbidity and preventing potential mortality. Blood bankers should be promptly consulted by the treating physician in patients with an acute fall in Hb level following recent transfusion(s). Furthermore, we consider that clinicians should have basic knowledge of the signs and symptoms of DHTR, so that DHTR will be appropriately diagnosed and the correct treatment administered.

To raise clinicians' awareness for improved recognition and reporting of DHTR, we recommend that education for DHTR should be part of medical school education and hospital grand round conferences.

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