



Case Report

Acute extravascular hemolytic transfusion reaction due to anti-Kpa antibody missed by electronic crossmatch [☆]



Ruth Padmore ^{*}, Philip Berardi, Kathy Erickson, Diana Desjardins, Antonio Giulivi, Melanie Tokessy, Doris Neurath, Elianna Saidenberg

Division of Hematopathology and Transfusion Medicine, The Ottawa Hospital and Eastern Ontario Regional Laboratory Association, 501 Smyth Road, Ottawa, Ontario K1H 8L6, Canada

ARTICLE INFO

Article history:

Received 16 March 2014
Accepted 11 August 2014

Keywords:

Acute extravascular hemolysis
Anti-Kpa antibody
Electronic crossmatch

ABSTRACT

Background: Kpa antigen is a low incidence red blood cell antigen within the Kell system. Anti-Kpa alloantibody may be associated with acute and delayed hemolytic transfusion reactions.

Case Study: We report a case of a clinically significant acute extravascular hemolytic transfusion reaction mediated by previously unrecognized (and undetected) anti-Kpa alloantibody. This reaction occurred in a patient who met all criteria for electronic crossmatch, resulting in the transfusion of an incompatible red cell unit.

Results: Post-transfusion investigation showed the transfused red cell unit was crossmatch compatible at the immediate spin phase but was 3 + incompatible at the antiglobulin phase. No evidence of intravascular hemolysis was observed upon visual comparison of the pre- and post-transfusion peripheral blood plasma. Further testing showed the presence of anti-Kpa antibody. The clinical course of the patient included acute febrile and systemic reaction.

Conclusion: Acute extravascular hemolytic transfusion reaction may occur due to undetected anti-Kpa alloantibody. Various strategies for crossmatching are discussed in the context of antibodies to low incidence antigens.

© 2014 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/3.0/>).

1. Introduction

The Kpa antigen (KEL3, Penney) is a low incidence red blood cell antigen within the Kell system. Only approximately 2% of blood donors are Kpa positive [1]. Antibodies against antigens within the Kell system are usually IgG type and acquired through exposure to antigen positive red blood cells during pregnancy or transfusion, although the antibody may occasionally be naturally occurring, as was the case in the original description of this antibody [2]. Anti-Kpa alloantibody is known to be clinically significant

and associated with both acute and delayed hemolytic transfusion reactions as well as hemolytic disease of the fetus and newborn (HDFN) [2–4]. Given the rarity of the Kpa antigen, antibodies to this antigen are not common.

Computer-assisted electronic crossmatching is standard practice in many transfusion laboratories if specific requirements are met [5]. The recipient must not have any evidence of clinically significant antibodies, presently or in the past. At least two concordant results of ABO and RhD typing must be on record, including one from the current sample. Additional laboratory information system requirements must also be met. When electronic crossmatching is performed neither an immediate spin nor antiglobulin phase crossmatch between recipient plasma and donor red cells is required. Electronic crossmatch has cost–benefits and is safe for most patients. However, it is known that potential clinically significant antibodies, including antibodies to

[☆] Sources of support: none.

^{*} Corresponding author. Tel.: +1 613 737 8899 ext 71733; fax: +1 613 739 6101.

E-mail address: rpadmoredottawahospital.on.ca (R. Padmore).

low incidence antigens may be missed by electronic crossmatch [6].

We report here a case of a clinically significant acute extravascular hemolytic transfusion reaction mediated by previously unrecognized (and undetected) anti-Kpa antibody in a patient who met all criteria for electronic crossmatch, resulting in the transfusion of an incompatible red cell unit.

2. Case report

A 64 year old clinically obese female with diabetes and previous history of myocardial infarction was admitted for urgent repair of a hiatal hernia. The patient had two previous pregnancies. The patient had remote history of transfusion in the 1980s through which she acquired hepatitis C. The patient had a more recent history of red cell transfusion with one unit of red cells transfused after gastrointestinal bleeding 5 years earlier at which time no antibodies were identified.

The patient was blood group O, RhD positive. At the time of current presentation, the antibody screen was negative. The hemoglobin was 82 g/L pre-transfusion. One unit of group O, RhD positive, leukoreduced packed red blood cell (PRBC) unit was issued to the patient after electronic crossmatch indicated compatibility. During the transfusion, the patient experienced an elevation in temperature, from 37.9 °C pre-transfusion to 39.5 °C during transfusion, accompanied by chills/rigors, and soon followed by shortness of breath. The transfusion was permanently discontinued. At this point the patient had received about 200 mL of PRBCs.

Immediately after the transfusion the hemoglobin was 90 g/L. The patient was given supplemental oxygen, bronchodilator (salbutamol) and bilevel positive airway pressure (BPAP) ventilatory support for a few hours. The patient's signs and symptoms resolved within a few hours with no additional intervention. Patient blood cultures and cultures of the remainder of the PRBC unit were negative. Transient elevation of the total bilirubin and lactate dehydrogenase was noted (Fig. 1). Transient elevation of troponin I was observed following the incompatible red cell transfusion, peaking just before the surgery (Fig. 2). EKG performed before the incompatible red cell transfusion showed old anterior myocardial infarct. EKG performed after the surgery showed atrial fibrillation and evidence of new inferior wall ischemia. No EKG was performed in the interval after the incompatible red cell transfusion and before the surgery. One day after receiving the incompatible PRBC unit, the patient underwent laparoscopic reduction of the hiatal hernia and gastrostomy tube insertion without incident.

On post-operative day 2 the hemoglobin was noted to be 83 g/L. Two Kpa-negative PRBC units were found to be compatible with the patient's plasma at the anti-globulin phase crossmatch. One unit was transfused with no reaction. The patient was discharged from hospital one week after surgery in stable condition.

3. Materials and methods

For all transfusion testing, an appropriately identified EDTA tube of peripheral blood was obtained from the patient. ABO and RhD typing was performed using

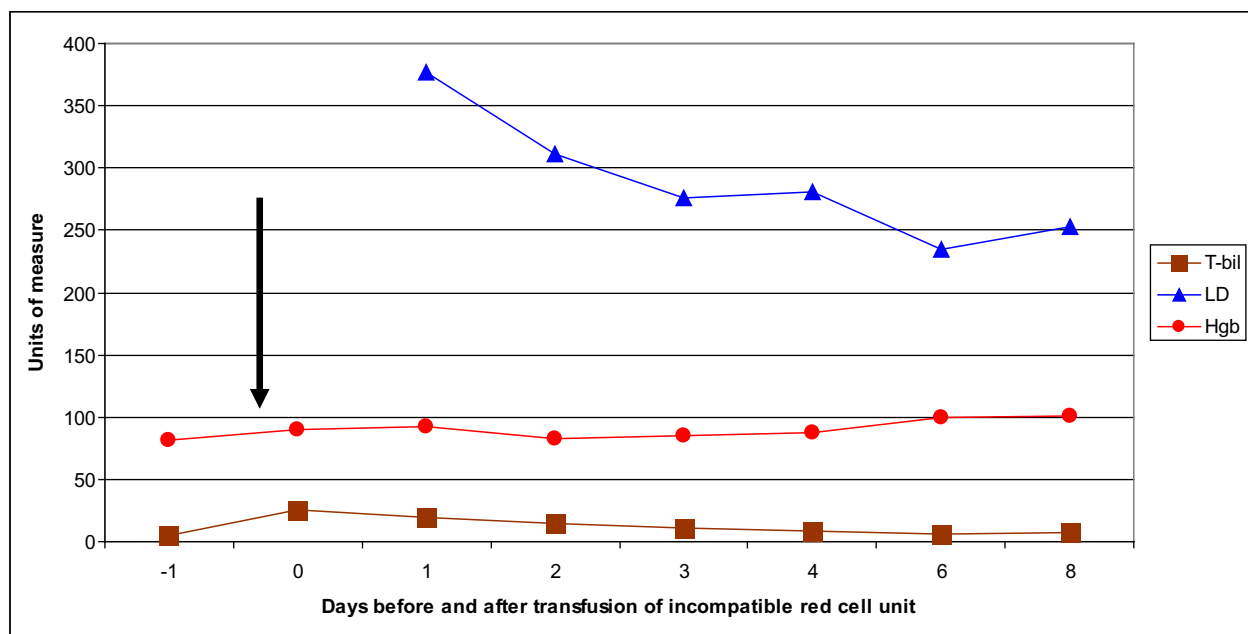


Fig. 1. Laboratory values from the day before to 8 days following transfusion of incompatible red cell unit. Black arrow indicates when incompatible transfusion occurred. (Hgb = hemoglobin g/L, LD = lactate dehydrogenase U/L, T-bil = total bilirubin umol/L).

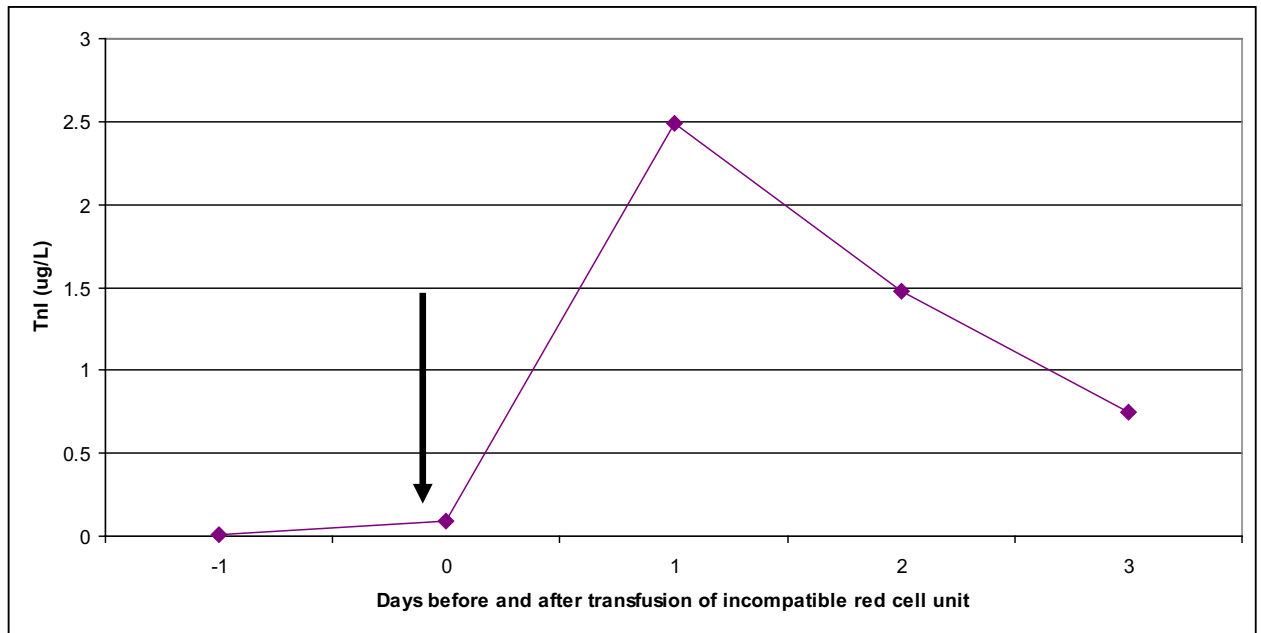


Fig. 2. Troponin I results from the day before to 3 days following transfusion of incompatible red cell unit. Black arrow indicates when incompatible transfusion occurred. Note that the peak Troponin I level of 2.49 µg/L was observed before the surgery for hiatal hernia repair.

microplate technology on the Galileo Neo instrument (Immucor Inc. Norcross, GA, USA). A three cell antibody screen was performed by solid phase technology using the CAPTURE-R READY-SCREEN (3), Lot No. R311 (Immucor Inc, Norcross). A red cell unit was assigned to the patient using the electronic crossmatch validated to be compliant with published standards [7].

Laboratory testing for the investigation of the reported transfusion reaction was performed in keeping with standard methodologies [5]. An immediate spin crossmatch was performed by adding two drops of patient post-transfusion plasma to an empty tube with one drop of 3% red cell suspension prepared from the implicated donor red cell unit segment. After mixing, the tube was centrifuged at 3400 rpm for 15 seconds. The solution was examined for hemolysis. The red cell button was resuspended and read macroscopically for agglutination. As no agglutination or hemolysis was observed the test was reported as negative.

The test was continued to the antiglobulin phase by adding two drops PEG reagent to the tube and incubating at 37 °C for 15 minutes. The solution was washed four times. Two drops of anti-IgG were added, gently mixed and then centrifuged at 3400 rpm for 15 seconds. Immediately after centrifugation the cells were resuspended and read macroscopically. The antiglobulin crossmatch was incompatible with grade 3 agglutination.

A direct antiglobulin test (DAT) was performed by washing one drop of the patient 3% red cell suspension to a dry cell button and then adding two drops of polyspecific antihuman globulin reagent. After mixing the tube was centrifuged at 3400 rpm for 15 seconds. Immediately after centrifugation the cells were resuspended and examined both macroscopically and microscopically. The polyspecific

DAT was reported as weakly positive (microscopic). Differential DAT testing was performed by the same technique using monospecific reagents. The anti-IgG showed a weakly positive result and anti-C3 was weakly positive only after 5 minute room temperature incubation.

4. Results

Prior to the first (incompatible) PRBC transfusion the patient was typed as group O, Rh positive, consistent with the patient's historical blood group on file. No history of pre-existing antibodies was known and the pre-transfusion antibody screen was negative using a three-cell panel. One unit of PRBCs was selected using electronic crossmatch and was visually inspected to confirm suitability for transfusion.

Following the febrile transfusion reaction, a clerical check was performed, and no errors were found, with the name and identification numbers and donor unit numbers and labels identical on all specimens and request forms. The pre- and post-transfusion peripheral blood specimens were visually inspected for hemolysis, and no evidence of hemolysis in the plasma was observed (Fig. 3). The post-transfusion crossmatch was compatible at the immediate spin phase, but was 3+ incompatible at the antiglobulin phase. DAT testing was performed on the pre-transfusion sample and found to be negative. However, DAT on a post-transfusion sample was weakly positive for anti-IgG. The anti-C3 DAT was negative at time = 0, but then found to be weakly positive after 5 minutes of incubation at room temperature. The transfused red cell unit was typed as Kpa positive. The patient's pre-transfusion red cells were phenotyped and shown to be Kpa negative. Extended

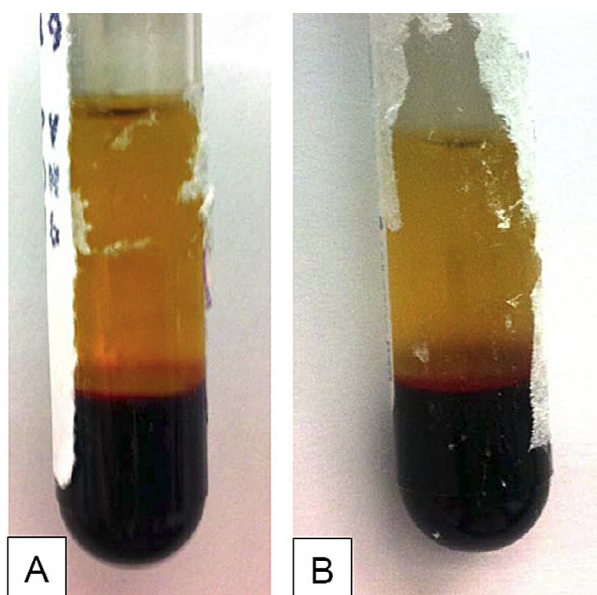


Fig. 3. (A) Pre-transfusion plasma. (B) Post-transfusion plasma. No hemolysis noted.

antibody investigation using the post-transfusion plasma sample showed 3 + positive reaction with Kpa positive cells. No other red cell antibodies were identified.

5. Discussion

Kpa is a low frequency antigen of the Kell system [1]. Antibodies to Kpa usually develop following transfusion or through fetal-maternal immunization, but may be naturally occurring [1]. Delayed hemolytic transfusion reaction and hemolytic disease of the fetus or newborn due to anti-Kpa are usually only mild to moderate; however one case of severe delayed hemolytic transfusion reaction has been reported [3].

The risk of acute hemolytic transfusion reaction due to missed antibody to low frequency antigen has been estimated at 1 per 650,000 crossmatches using immediate spin or electronic crossmatch technology [8]. Two recent studies have identified anti-Kpa in 3% and 4.7% of patients requiring chronic transfusion therapy who have alloantibodies to red cells [9,10]. Kpa antigen is present in approximately 2% of Caucasians [1]. If this antigen frequency if multiplied by the antibody frequency listed above, it can be calculated that incompatibility will be encountered in up to 0.094% or approximately 1 in 1000 transfusions in this population. However, it should be noted, that since allo-immunized patients are not eligible for electronic or immediate spin crossmatching, anti-Kpa antibody is unlikely to be missed in this population.

Electronic crossmatch is a safe and effective method for selection of red cells for transfusion, and carries a similar risk of missing low incidence antibodies as immediate spin

crossmatch techniques. As such antibodies generally do not cause severe hemolytic transfusion reactions this risk is readily accepted by most transfusion services [6]. However acute extravascular hemolytic transfusion reaction may be associated with fever due to acute cytokine release [11], and may stress an already vulnerable patient, as in this case report, where the patient had significant co-morbidities, and exhibited a transient elevation of troponin I following transfusion of the incompatible red cell unit.

An option to ensure that the transfusion service avoids missing antibodies to low incidence antigens may be to include testing red cells with low incidence antigens in pre-transfusion antibody screening. This may be an approach suitable for reference transfusion medicine laboratories and suggested antigens may include Vel, Jsa, Deigo, Cw, Wra and Kpa. This has the advantage of avoiding acute hemolytic transfusion reactions due to missed alloantibodies, but has the disadvantage of added time and expense. In an ideal world, transfusion requisitions would contain a wealth of relevant clinical information to enable laboratories to select appropriate patients in whom to perform this extended testing. Computer provider order entry (CPOE) may be a tool that will enable this and it is important for transfusion specialists to advocate for technologies that will allow the safest, yet most fiscally responsible testing algorithms in their hospitals [12]. Until such utopian visions for transfusion testing and therapy are achieved, it is important to report cases such as these that may assist others in timely identification and management of similar transfusion reactions, and enable reflection on the various strategies for antibody identification and crossmatching policies and procedures and their impact on patient care.

References

- [1] Reid ME, Lomas-Francis C. *The blood group antigen facts book*. 2nd ed. Elsevier; 2004.
- [2] Allen FH Jr, Lewis SH. Kpa (Penney), a new antigen in the Kell blood group system. *Vox Sang* 1957;2:81–7.
- [3] Koshy R, Patel B, Harrison JS. Anti-Kpa-induced severe delayed hemolytic transfusion reaction. *Immunohematology* 2009;25:44–7.
- [4] Jensen KG. Haemolytic disease of the newborn caused by anti-Kpa. *Vox Sang* 1962;7:476–8.
- [5] Judd WJ. Requirements for the electronic crossmatch. *Vox Sang* 1998;74:409–17.
- [6] Garratty G. How concerned should we be about missing antibodies to low incidence antigens? *Transfusion* 2003;43:844–7.
- [7] Standard Work Instruction Manual (SWIM Manual). Ontario regional blood coordinating network (ORBCoN). 2009 September 1.
- [8] Shulman IA. The risk of an overt hemolytic transfusion reaction following the use of an immediate spin crossmatch. *Arch Pathol Lab Med* 1990;114:412–4.
- [9] Azarkeivan A, Ansari S, Ahmadi MH, Hajibeigy B, Maghsudlu M, Nasizadeh S, et al. Blood transfusion and alloimmunization in patients with thalassaemia: a multicenter study. *Pediatr Hematol Oncol* 2011;28:479–85.
- [10] Duboeuf S, Flourie F, Courbil R, Benamara A, Rigal E, Cognasse F, et al. [Identification of alloantibodies and their associations] (French). *Transfus Clin Biol* 2012;19:358–65.
- [11] Davenport RD. Pathophysiology of hemolytic transfusion reaction. *Semin Hematol* 2005;42:165–8.
- [12] Dzik WH. Technology for enhanced transfusion safety. In: *ASH education program book*. 2005. p. 476–82.