A fatal case of acute hemolytic transfusion reaction caused by anti-Wr\textsuperscript{a}: case report and review of the literature

A. Espinosa, L.J. Garvik, N. Trung Nguyen, and B. Jacobsen

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Case Report

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The red blood cell (RBC) antigen Wr\textsuperscript{a} is a low-prevalence antigen first described in 1953 by Holman and assigned to the Diego system in 1995. Because of its low prevalence, Wr\textsuperscript{a} is usually absent on commercial screening RBCs and antibody identification panels. When Wr(a+) screening RBCs are available, the corresponding antibody, anti-Wr\textsuperscript{a}, is often found in sera from healthy individuals, patients, and pregnant women. Anti-Wr\textsuperscript{a} can cause both hemolytic transfusion reactions and hemolytic disease of the fetus and newborn. We describe a fatal acute hemolytic transfusion reaction caused by anti-Wr\textsuperscript{a} in a patient with no other RBC alloantibodies. Serologic investigation showed that one of the RBC units the patient received was Wr(a+). Immunohematology 2021;37:20–24.

Key Words: low-prevalence antigen, Wr\textsuperscript{a}, hemolysis, acute hemolytic transfusion reaction, crossmatch

Wr\textsuperscript{a} is the most common low-prevalence antigen (LPA) in the white population, and anti-Wr\textsuperscript{a} is the most common naturally occurring antibody.\textsuperscript{1} The first case of anti-Wr\textsuperscript{a} was described by Holman\textsuperscript{2} in 1953 in a child with severe hemolytic disease of the fetus and newborn (HDFN), requiring exchange transfusion. Anti-Wr\textsuperscript{a} is often identified when Wr(a+) red blood cells (RBCs) are available on the screening or identification panel RBCs, but the antibody is otherwise rarely involved in serious hemolytic transfusion reactions (HTRs) or HDFN, other than in isolated case reports.\textsuperscript{3–12} There is, therefore, high consensus in the transfusion community regarding the lack of justification for the inclusion of Wr(a+) RBCs on commercial screening and panel RBCs.\textsuperscript{13–15}

The prevalence of Wr\textsuperscript{a} has been estimated to be 0.064 percent (1 in 1570) in Norwegian blood donors,\textsuperscript{16} 1 in 1000 in the British population, and 1 in 785 in the Spanish population.\textsuperscript{17} In a study of Brazilian blood donors,\textsuperscript{18} the prevalence of Wr\textsuperscript{a} was estimated to be 1 in 1662. The authors found that the prevalence of anti-Wr\textsuperscript{a} was 1 in 31, similar to that found in Spanish blood donors, but higher when compared with other studies.\textsuperscript{13,19} In different patient settings, the prevalence of anti-Wr\textsuperscript{a} is much higher, such as in antibody-induced hemolytic anemia,\textsuperscript{20} where anti-Wr\textsuperscript{a} can be found in 1 in 2 to 1 in 3 patients with autoimmune hemolytic anemia.\textsuperscript{21}

Based on the low prevalence of Wr\textsuperscript{a}, Wr\textsuperscript{a} incompatibility in the European population is expected to occur in ~1 in 150,000 RBC transfusions.\textsuperscript{12}

Wr\textsuperscript{a} is fully developed at birth, but anti-Wr\textsuperscript{a} is otherwise rarely involved in HDFN. This finding may be because the majority of cases of anti-Wr\textsuperscript{a} are naturally occurring and, when found, are sometimes automatically assumed to be low titer, cold reacting, and IgM in class and, therefore, are dismissed as being unable to cross the placenta and cause fetal RBC destruction. However, studies have shown that anti-Wr\textsuperscript{a} often includes both IgG and IgM.\textsuperscript{1} Wr\textsuperscript{a} is resistant to the treatment of RBCs with dithiothreitol and proteolytic enzymes such as papain, trypsin, and ficin. Arriaga et al.\textsuperscript{17} showed that 51 percent of anti-Wr\textsuperscript{a} identified in pregnant women and patients were of immunoglobulin subclass IgG1 or IgG3, which are potentially clinically significant. The same authors\textsuperscript{17} found that anti-Wr\textsuperscript{a} found in healthy donors is predominantly an IgM antibody with or without an associated IgG component.

Anti-Wr\textsuperscript{a} is an intriguing antibody, since it differs from antibodies against other LPAs in its high prevalence, even in patients never transfused or with no known history of pregnancy.\textsuperscript{19} It is believed that the nature of the antibody can be both natural and immune-mediated. Naturally occurring anti-Wr\textsuperscript{a} can be identified with different frequencies in healthy individuals, in pregnancy, and in patients, with especially high frequency in patients with autoimmune hemolytic anemia\textsuperscript{20} and in previously allo-immunized pregnant women.\textsuperscript{21}

We describe a fatal HTR caused by anti-Wr\textsuperscript{a} in a 91-year-old white female patient.

Case Report

A 91-year-old white woman was admitted to the hospital after being found on the floor in her home, disoriented and complaining of pain in her right hip. She had a medical history...
of hypertension, hypercholesterolemia, glaucoma, chronic renal insufficiency, and esophagitis, among other medical conditions. The radiologic investigations after admission showed a pertrochanteric fracture in her right hip, and she was operated on the same day with osteosynthesis. The day after surgery, her hemoglobin (Hb) level fell from 11.5 to 8.0 g/dL (normal range 12.0–14.7 g/dL) (Fig. 1), and 2 RBC units were issued by electronic crossmatch, since the patient’s antibody detection test was negative, and she had no known RBC antibodies. The first RBC unit was transfused without any complication, but when approximately half of the second unit had been transfused, the patient started to feel unwell. She experienced chills, nausea, arrhythmia, and tachycardia (200 beats per minute [bpm]; normal range 60–100 bpm). Her body temperature rose from 37 to 38.1°C, and her O₂ saturation level dropped to 75 percent (normal >95%). The transfusion was immediately stopped, and the patient was transferred to the intensive care unit. The blood gas analysis showed reduced PO₂ and increased lactate, and the blood samples taken right after the transfusion reaction showed visible hemolysis. Laboratory tests showed normal haptoglobin, increased total bilirubin (TB), high levels of lactate dehydrogenase (LDH), and increased creatinine (Table 1). After stabilization and observation for 5 hours, the patient was moved back to the ward.

![Fig. 1 Hemoglobin (Hb) levels (g/dL) before and after the transfusion reaction. 1 = day of admission to the hospital and surgery; 2 = day of transfusion (red arrow); 6 = day of death.](image)

The day after the transfusion, the patient was improving clinically except for a persistent reduced diuresis from before the transfusion (75 mL during the night) and hematuria. The patient received intravenous (IV) fluids, noradrenalin, and diuretics. The response to the initial dose of diuretics was not adequate, and an increased dose was given to the patient (500 mg IV infusion during the day), which still did not yield the desired response. On day 3 after the transfusion, the patient’s clinical condition started to worsen significantly. In spite of the treatment with IV fluids and diuretics, the patient continued to show almost absent diuresis (<30 mL diuresis per hour after 3 L fluids IV). On day 4 after the transfusion, the patient’s condition deteriorated further, and the patient was barely conscious. At that point, her Hb level had dropped to 6.4 g/dL. Biochemical investigations at this point showed decreasing levels of TB and LDH, but creatinine levels were increasing up to 540 µmol/L, ~63 hours after the transfusion (Table 1). The patient was not considered a candidate for dialysis because of her numerous comorbidities, and she, along with her closest family members, was informed of the severity of her condition. At this point, active supportive care was terminated. She passed away ~90 hours after the transfusion, likely because of extensive renal failure caused by the HTR.

### Results

The initial serologic workup for suspected HTR was performed at the local blood bank, and it included immediate spin (IS) and indirect antiglobulin test (IAT) crossmatches. The patient’s ABO group, as well as the ABO group of the 2 blood units, was confirmed to be correct. The patient was group A, D–. The first RBC unit transfused was group O, D–, and the second unit was group A, D–. The patient’s post-transfusion sample showed hemolysis not present in the pre-transfusion sample. The antibody screening and identification tests, as well as the direct antiglobulin test (DAT), were negative in both pre- and post-transfusion samples (Table 2). On the other hand, both the IS and IAT crossmatches showed a positive reaction with the second unit in the pre- and post-transfusion samples (Figs. 2 and 3). The IS and IAT crossmatches were negative when tested with the first RBC unit in both pre- and

<table>
<thead>
<tr>
<th>Table 1. Biochemical parameters</th>
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<tbody>
<tr>
<td>Parameter</td>
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<tr>
<td>Creatinine, µmol/L</td>
</tr>
<tr>
<td>Bilirubin, µmol/L</td>
</tr>
<tr>
<td>Lactate dehydrogenase, U/L</td>
</tr>
<tr>
<td>Haptoglobin, g/L</td>
</tr>
<tr>
<td>Creatine kinase, U/L</td>
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<tr>
<td>D-dimer, mg/L</td>
</tr>
</tbody>
</table>

Table 1. Biochemical parameters

*Number of hours after transfusion of second red blood cell unit.
†Normal value for the patient’s age.
NP = not performed.
post-transfusion samples (Table 2). Blood samples from the patient and the two blood donors were sent to our National Reference Laboratory in Blood Group Serology for further investigation, and we confirmed the results obtained by the local blood bank. Further investigation showed that the antibody had both an IgM and IgG component, with titers of 32 and 1024, respectively (Table 2). Taking the initial results into consideration, we suspected that the patient was immunized against an LPA not present on the screening RBCs or on the identification panels. Several antibodies against LPAs were excluded, such as anti-Jn\textsuperscript{a}, anti-Wu, anti-Vw, anti-Di\textsuperscript{i}, and anti-Ny\textsuperscript{a}. Because of a clerical error at our laboratory, the blood donor involved in the positive IS crossmatch reaction was erroneously typed as Wr(a–), while the patient was typed as Wr(a+), resulting in anti-Wr\textsuperscript{a} being initially excluded as the cause of the HTR. Further investigation was considered necessary, and blood samples from the patient and both donors were sent to the International Blood Group Reference Laboratory (IBGRL) in Bristol, UK. The results provided by the IBGRL confirmed the presence of anti-Wr\textsuperscript{a} in the patient’s plasma, as well as the phenotype Wr(a+b+) in 1 of the 2 donor units. No other RBC antibodies were present in the patient’s plasma.

The patient had no known history of pregnancies. According to the patient’s hospital records, she had only been transfused once, in 2001, because of an operation for abdominal lipoma. She received 2 RBC units with no complications. Her RBC antibody detection test was also negative at that point. In an attempt to determine if the patient could have been immunized by her previous RBC transfusion, we were able to obtain blood samples from the two blood donors from whom the patient had received transfusions in 2001. Both donor samples were typed as Wr(a–), and the IS crossmatches between the patient and the donors were negative.

**Discussion**

We report the serologic findings and the clinical outcome in a 91-year-old white female patient experiencing a fatal HTR caused by anti-Wr\textsuperscript{a}.

### Table 2. Immunohematologic results

<table>
<thead>
<tr>
<th>Test parameter</th>
<th>Patient</th>
<th>RBC unit 1</th>
<th>RBC unit 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO, D</td>
<td>A, D–</td>
<td>O, D–</td>
<td>A, D–</td>
</tr>
<tr>
<td>Wr\textsuperscript{a} phenotype</td>
<td>Wr(a–)</td>
<td>Wr(a–)</td>
<td>Wr(a+b+)</td>
</tr>
<tr>
<td>Anti-Wr\textsuperscript{a} titer</td>
<td>IgM 32, IgG 1024</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Antibody detection test</td>
<td>Negative\textsuperscript{*}</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Initial antibody identification</td>
<td>Negative\textsuperscript{*}</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>DAT</td>
<td>Negative\textsuperscript{*}</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>IS crossmatch</td>
<td>NA</td>
<td>Negative</td>
<td>Positive (4+)\textsuperscript{*}</td>
</tr>
<tr>
<td>IAT crossmatch</td>
<td>NA</td>
<td>Negative</td>
<td>Positive (4+)\textsuperscript{*}</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Results pre-transfusion reaction.

\textsuperscript{†}Results post-transfusion reaction.

RBC = red blood cell; Ig = immunoglobulin; NA = not applicable; DAT = direct antiglobulin test; IS = immediate spin; IAT = indirect antiglobulin test.

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**Fig. 2** Immediate spin crossmatch results of the Wr(a+) red blood cell (RBC) donor unit. (A) Pre-transfusion. (B) Post-transfusion. \textsuperscript{*}RBCs from the blood tube after RBC unit transfusion. \textsuperscript{†}RBCs from the RBC unit. (Strength of reaction: 4+ [maximum] to 0 [negative]; 0.5+ = weak positive.)

**Fig. 3** Indirect antiglobulin test crossmatch results of the Wr(a+) red blood cell (RBC) donor unit. (A) Pre-transfusion. (B) Post-transfusion. \textsuperscript{*}RBCs from the blood tube after RBC unit transfusion. \textsuperscript{†}RBCs from the RBC unit. (Strength of reaction: 4+ [maximum] to 0 [negative].)
The implementation of the widely used “type and screen” approach for pre-transfusion testing, introduced in 1984, led to an increased risk for HTRs due to antibodies against LPAs. LPAs can be defined as antigens occurring in <1 percent of the population. The overall risk for an HTR caused by an LPA was calculated by Garratty22 to be ~1 in 500,000 transfusions and deemed to be acceptably low enough to justify the absence of LPAs such as Wr(a+) on the routine screening RBCs.23

Wallis et al.13 observed a higher incompatibility incidence of 1 in 10,700 incompatible units due to anti-Wr(a+) in 1199 hospital patients. The same authors13 propose three possible strategies to manage potential patients with anti-Wr(a+): (1) to perform full compatibility testing on all units before transfusion, (2) to assume that the risk for HTR caused by anti-Wr(a+) is so small that it may be ignored and the IS crossmatch or the computer-guided blood selection can be used, or to type all donors for Wr(a+) and then perform full compatibility testing when selecting Wr(a+) units for transfusion. The first strategy is not in use in Norway after the implementation of the computer crossmatch in the late 1990s. The second alternative is the general current strategy regarding anti-Wr(a+) and other LPAs, while the third strategy may not be technically possible for some blood bank computer systems. Even if the risk of a serious HTR due to anti-Wr(a+) is very low, the high incidence of the antibody in the patient setting may require the implementation of preventive measures. Special consideration should be taken regarding the management of Wr(a+) blood donors. A possible strategy, the one we propose, is to type all first-time donors for Wr(a+) and then permanently exclude Wr(a+) donors from RBC transfusion purposes. There are no current national recommendations in Norway regarding the typing of donors for LPAs such as Wr(a+), Kp(a+), or Co(a+), or any recommendation regarding the management of these donors.

Wr(a+) donors could still be accepted as plasmapheresis or platelepheresis donors. In addition, they may become “technical donors,” as a source of Wr(a+) RBCs. Because the prevalence of Wr(a+) in the general population is very low, this measure should not be expected to have a deleterious effect on blood donor recruitment. The Wr(a+) blood donor in this case report was a first-time donor, and no look-back was therefore possible regarding the likelihood of hemolytic reactions in other patients. For precautionary reasons, the donor was permanently deferred. Our patient had both IgM and IgG antibodies (Table 2), and the relatively high IgG titer was unexpected, bearing in mind that the antibody was likely to be naturally occurring. Other causes of immunization therefore cannot be excluded. The reaction strength of the IS testing differed significantly in the samples taken before and after the reaction, indicating a high degree of hemolysis of the transfused Wr(a+) unit (Fig. 2). The negative DAT in the post-transfusion sample was also in accordance with hemolysis (Table 2). The strength of the IAT crossmatch was also reduced in the post-transfusion sample, but to a lesser extent than the IS crossmatch (Fig. 3).

Anti-Wr(a+) is not the only potentially clinically significant antibody against LPAs. Even if several examples of HTRs caused by other antibodies against LPAs have been reported, the computer crossmatch is considered to be a safe approach for selecting blood units for non–allo-immunized patients. On the other hand, this case highlights the importance of an extensive serologic investigation, including the IS crossmatch, when an HTR is highly suspected, even if the RBC antibody detection test and DAT show negative results. In Norway, it is common practice to issue RBC units by crossmatch when an HTR is suspected and until the immunohematologic workup is completed. This practice is recommended even if the patient had a negative antibody detection test before the transfusion. Once the immunohematologic workup can rule out an alloantibody as the cause of the reaction, the RBC units may once again be issued by electronic crossmatch.

Several examples of HTRs caused by anti-Wr(a+) have been described but, to our knowledge, only a few fatalities have been reported.3,12 The hemovigilance system in the UK (Serious Hazards of Transfusion [SHOT])25 described 10 cases of HTRs due to anti-Wr(a+) in the period from 2008 to 2011, and one of these cases had a fatal outcome. Two further cases, one acute and one delayed hemolytic transfusion reaction (DHTR) caused by anti-Wr(a+), were reported in the annual report26 for 2017, and three cases of DHTR were reported in the 2019 annual report.27 In the Norwegian hemovigilance system28,29 Troll, two cases of acute HTRs due to anti-Wr(a+) have been reported since 2004, in addition to the one described in this case report. Neither of the two previous cases had a fatal outcome.

The case described here presents an opportunity to remind clinicians of the risks of RBC transfusion, even when the patient has a negative antibody detection test, and it highlights the importance of early recognition of symptoms characteristic of an HTR.

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