CASE REPORT

Acute hemolytic transfusion reaction attributed to anti-At^a

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Anti-At^a is a rare alloantibody that can be clinically significant. We report a case of a woman who, after emergency-released uncrossmatched red blood cell transfusion, experienced an acute hemolytic transfusion reaction attributed to anti-At^a. The case presented herein highlights the importance of recognizing that anti-At^a may indeed cause acute hemolytic reactions. ***Immunohematology*** **2016;32:140–142.**

Key Words: anti-At^a, high-prevalence antigen, hemolytic transfusion reaction

Anti-At^a is directed at the At^a (Augustine) antigen, a high-prevalence red blood cell (RBC) antigen present in greater than 99 percent of people in all populations.[1] Individuals lacking the At^a antigen, who can potentially make anti-At^a, often originate from the Caribbean or Southern United States.[1] The At^a antigen and corresponding antibody were first described by Applewhaite and colleagues in 1967 after a weakly positive direct antiglobulin test (DAT) was incidentally discovered in an infant of a multiparous black woman of West Indian origin named Mrs. August.[2] There was no laboratory or clinical evidence of hemolytic disease of the fetus and newborn (HDFN) during any of her three pregnancies. Subsequent population analyses have demonstrated reactivity of anti-At^a with RBCs of at least 6600 random New Yorkers (including at least 2200 individuals of African ancestry),[2] at least 3000 random blood donors,[3] and 8551 out of 8552 people living in Detroit, Michigan, of African ancestry[4]—thus establishing the high prevalence of At^a.

There have been several published reports describing anti-At^a, totaling 14 patients in all, but only a subset of these patients have experienced an adverse reaction after RBC transfusion attributed to anti-At^a (Table 1). The reported adverse reactions

Table 1. Reported cases of anti-At^a

Case[reference]	Gender	Age	Race	ABO group	Previous transfusion	Previous pregnancy	Adverse reaction
1[2]	Female	Unknown	Black	B	No	Yes	DAT+ in newborn
2[3]	Female	40	Black	A	No	Yes	No
3[5]	Male	65	Black	O	Yes	—	Chills
4[5]	Female	26	Black	O	No	Yes	No
5[5]	Female	34	Black	AB	Yes	Yes	No
6[5]	Female	39	Black	B	No	Yes	Unknown
7[5]	Female	44	Black	B	Unknown	Yes	DAT+ in newborn
8[5]	Female	35	Black	B	No	Yes	No
9[6]	Female	Unknown	Black	B	Unknown	Yes	DAT+ in newborn; decreased 24-hour RBC survival study (2 mL)
10[7]	Female	26	Black	O	Yes	No	Fever, chills, nausea associated with decreased 3- and 19-hour RBC survival study (5 mL)
11[7]	Female	36	Black	A	No	Yes	DAT+ in newborn
12[8]	Female	35	Black	A	Unknown	Yes	HDFN
13[9]	Female	60	Black	Unknown	No	Yes	DHTR
14[10]	Female	37	Black	AB	No	Yes	No
15*	Female	40	Black	O	No	Yes	AHTR

*Patient described in the current report.

DAT = direct antiglobulin test; RBC, red blood cell; HDFN = hemolytic disease of the fetus and newborn; DHTR = delayed hemolytic transfusion reaction; AHTR = acute hemolytic transfusion reaction.

in this population include positive DAT in newborns,[2,5,6] chills,[5,7] fever,[7] nausea,[7] decreased RBC survival,[6,7] a moderate case of HDFN,[8] and, most recently, a case of severe delayed hemolytic transfusion reaction.[9] Nonetheless, until now, no acute hemolytic transfusion reaction associated with transfusion of an At(a+) RBC unit has been described. We report a case in which a clinically significant acute hemolytic transfusion reaction was attributed to anti-At^a.

Materials and Methods

All data were retrospectively collected from the patients' medical records. This review was approved by the Quality Council of the Institute for Transfusion Medicine (Pittsburgh, PA). ABO and D testing were performed using solid-phase technology (Galileo, Immucor, Inc., Norcross, GA). All additional immunohematology testing was performed using saline tube methods with reactions graded on a scale of 0 to 4+. Additional reagents used included low-ionic-strength saline (LISS), polyspecific (anti-IgG/anti-C3d) antihuman globulin (AHG), monospecific anti-IgG AHG, monospecific anti-C3d AHG, and acid elution kit (all obtained from Immucor, Inc.).

Case Report

A 40-year-old black woman with history of autoimmune hypothyroidism, three uneventful pregnancies, and no history of transfusion presented with fatigue and dyspnea on exertion. Her symptoms were secondary to megaloblastic anemia and severe vitamin B12 deficiency attributable to pernicious anemia that was positive for anti-intrinsic factor antibody. Her admission laboratory values included: hemoglobin 5.6 g/dL (normal 12.3–15.3 g/dL), platelet count 80,000/μL (normal 145,000–445,000/μL), lactate dehydrogenase (LDH) 4440 IU/L (normal 110–216 IU/L), total bilirubin 3.7 mg/dL (normal 0.2–1.2 mg/dL), and direct bilirubin 0.8 mg/dL (normal 0.0–0.4 mg/dL). Her ABO and D typings showed her RBCs to be group O, D+. Her antibody screen was positive, with all screening cells reacting 3+ at the AHG phase in tube testing with LISS enhancement. Because of her positive antibody screen, a DAT was performed, and it was negative with polyspecific AHG reagent; an eluate was performed and was also negative. Because of the patient's symptomatic anemia, the decision was made to emergently transfuse the patient, and two emergency-released uncrossmatched RBC units were issued. Approximately 15 minutes after the first RBC unit had been completely transfused, the patient developed chills and had one episode of dark urine, although she remained afebrile with stable vital signs.

A transfusion reaction workup was initiated. All elements of the clerical check were confirmed normal; these elements consisted of verification of (1) the blood bank issuing the proper blood product to the proper patient, (2) the unit number on the blood unit matching the unit number on the transfusion reaction form, (3) documentation of health care personnel having double-checked patient identification and blood product information prior to transfusion of the blood unit to the proper patient, and (4) patient identification on the post-transfusion blood sample and transfusion reaction form matching the blood bank records. Both the pre-transfusion and post-transfusion plasma specimens were icteric on visual inspection with no hemolysis noted. Biochemical tests of hemolysis were positive, including increased LDH (5669 IU/L), increased total bilirubin (7.1 mg/dL), increased direct bilirubin (2.2 mg/dL), and haptoglobin less than 10 mg/dL (normal 16–200 mg/dL). Repeat hemoglobin measurement demonstrated no post-transfusion increase from her pre-transfusion concentration (5.4 mg/dL). The DAT was now found to be weakly positive with polyspecific AHG reagent, negative with anti-C3d reagent, and weakly positive with anti-IgG AHG reagent. The eluate reacted with all screening cells at AHG phase (2+) except for the autocontrol. These findings suggested an alloantibody to a high-prevalence antigen had been detected, and anti-At^a was subsequently identified by a large immunohematology reference laboratory (Immunohematology Reference Laboratory, LifeShare Blood Centers, Shreveport, LA). The patient's RBCs were serologically typed for At^a and found to be negative. A differential adsorption using human erythrocyte stroma prepared from R_1R_1, R_2R_2, and rr cells of known phenotype was performed on the patient's serum to rule out the presence of any other underlying alloantibodies; none were identified. Two At(a–) RBCs units were obtained (one frozen unit immediately available from internal RBC inventory and one frozen unit available from regional blood donor center within 48 hours of request via the American Rare Donor Program), crossmatched, transfused without incident, and appropriately increased her hemoglobin level (pre-transfusion value 6.9 g/dL to post-transfusion value 8.9 g/dL).

Discussion

This case report describes a rare alloantibody, anti-At^a, which was implicated as a cause of a clinically significant acute hemolytic reaction. Immunohematology data from previous reports of anti-At^a have described it to be detectable with polyspecific and/or anti-IgG AHG reagents when bound to RBCs,[2,3,5,6,8–11] and in the vast majority of cases there has

been no complement bound to the RBCs as detected using routine anti-C3d monospecific AHG reagent.[1,8] The in vitro immunohematologic characteristics of anti-At^a described in this current report are consistent with those previously reported. Autoimmune disease has been posited[7] as having an association with development of anti-At^a—this proposed relationship is supported by the patient in the current report, who has two autoimmune diseases.

Recently, the genetic basis for the At(a–) phenotype has been discovered: a non-synonymous single nucleotide polymorphism in rs45458701 (c.1171G>A in exon 12 of *SLC29A1*) resulting in a non-conservative p.Glu391Lys substitution.[12] This finding has the potential to identify At(a–) donors and patients via RBC genotyping studies. Based on this evidence, the Augustine blood group system was formed (symbol AUG), and the At^a antigen was named AUG2 (number 036002).[13]

In conclusion, although anti-At^a is a rare antibody of variable clinical significance, it has the potential to cause rapid, acute, clinically significant hemolysis. If possible, patients who develop anti-At^a and require RBCs should be transfused with units negative for the cognate antigen.

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References

1. Reid ME, Lomas-Francis C, Olsson ML. The blood group antigen factsbook. 3rd ed. San Diego, CA: Academic Press, 2012:682.
2. Applewhaite F, Ginsberg V, Gerena J, Cunningham CA, Gavin J. A very frequent red cell antigen, At^a. Vox Sang 1967;13: 444–5.
3. Frank S, Schmidt RP, Baugh M. Three new antibodies to high-incidence antigenic determinants (anti-El, anti-Dp, and anti-So). Transfusion 1970;10:254–7.
4. Winkler MM, Hamilton JR. Previously tested donors eliminated to determine rare phenotype frequencies. International Society of Blood Transfusion/American Association of Blood Banks 1990 Joint Congress. Arlington, VA: American Association of Blood Banks, 1990:158.
5. Gellerman MM, McCreary J, Yedinak E, Stroup M. Six additional examples of anti-At^a. Transfusion 1973;13:225–30.
6. Sweeney JD, Holme S, McCall L, Huett D, Storry J, Reid M. At(a–) phenotype: description of a family and reduced survival of At(a+) red cells in a proposita with anti-At^a. Transfusion 1995;35:63–7.
7. Ramsey G, Sherman LA, Zimmer AM, et al. Clinical significance of anti-At^a. Vox Sang 1995;69:135–7.
8. Culver PL, Brubaker DB, Sheldon RE, Martin M, Richter CA. Anti-At^a causing mild hemolytic disease of the newborn. Transfusion 1987;27:468–70.
9. Cash KL, Brown T, Sausais L, Uehlinger J, Reed LJ. Severe delayed hemolytic transfusion reaction secondary to anti-At^a. Transfusion 1999;39:834–7.
10. Burnette RE, Couter K. A positive antibody screen—an encounter with the Augustine antibody. J Natl Med Assoc 2002;94:166–70.
11. Ramsey G, Smietana SJ. Multiple or uncommon red cell alloantibodies in women: association with autoimmune disease. Transfusion 1995;35:582–6.
12. Daniels G, Ballif BA, Helias V, et al. Lack of the nucleoside transporter ENT1 results in the Augustine-null blood type and ectopic mineralization. Blood 2015;125:3651–4.
13. Storry JR, Castilho L, Chen Q, et al. International Society of Blood Transfusion Working Party on Red Cell Immunogenetics and Terminology: report of the Seoul and London meetings. ISBT Sci Ser 2016;11:118–22.

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