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CASE SERIES

Clinical and Immunohematological Significance of Anti-Le^a, Anti-Le^b, and Anti-E Antibodies in Pre-Transfusion Testing

Anandan S,[1,*] Ashwin A,[2] Niranj Rathan R,[2] Krishnamoorthy R[3] and Sampat Kumar M[4]

[1]*Postgraduate, Department of Immunohematology and Blood Transfusion Medicine, Sri Ramachandra Medical College, Porur, Chennai*

[2]*Associate Professor, Department of Immunohematology and Blood Transfusion Medicine, Sri Ramachandra Medical College, Porur, Chennai*

[3]*Head of the Department, Department of Immunohematology and Blood Transfusion Medicine, Sri Ramachandra Medical College, Porur, Chennai*

[4]*Assistant Professor, Department of Immunohematology and Blood Transfusion Medicine, Sri Ramachandra Medical College, Porur, Chennai*

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Abstract

Background: Unexpected red cell antibodies detected during pretransfusion testing can pose significant challenges in transfusion management, particularly in obstetric patients. While some antibodies are clinically insignificant, others may lead to hemolytic transfusion reactions, necessitating careful immunohematological evaluation. **Case Presentation:** We report three cases of unexpected red cell antibodies detected during routine pretransfusion testing. In Case 1, a 28-year-old gravida 3 para 1 female with no prior transfusion history showed incompatible crossmatches, and further workup identified an Anti-Le^b antibody, with no transfusion required due to minimal blood loss. In Case 2, a 26-year-old primigravida at term with fetal distress demonstrated Anti-Le^a antibody during antibody screening. Despite its presence, one unit of PRBC compatible was transfused uneventfully during cesarean section, consistent with the typically clinically insignificant nature of Lewis antibodies. In Case 3, a 46-year-old multiparous female with a history of prior transfusions presented with abnormal uterine bleeding and was found to have anti-E alloantibody. **Results:** Two cases showed positive direct antiglobulin test (DAT) with negative autocontrol, suggesting alloimmunization. Lewis antibodies (anti-Le^a and anti-Le^b) were clinically insignificant and did not impact transfusion outcomes, whereas anti-E, a clinically significant Rh antibody, required careful antigen-matched transfusion support. **Conclusion:** These cases highlight the importance of comprehensive antibody screening and identification in pretransfusion testing. While Lewis system antibodies are usually benign, clinically significant antibodies such as anti-E necessitate antigen-negative blood selection to prevent hemolytic complications. Early detection and appropriate transfusion strategies are essential for ensuring patient safety.

Keywords: Alloantibodies, Anti-Lewis, Anti-E, Transfusion, Pregnancy

*Corresponding Author: Anandan S
Email: arunanandhan95@gmail.com

Introduction

Alloantibody formation following transfusion of blood products remains a clinically significant concern. Red blood cell (RBC) alloantibodies are particularly important, as they can adversely affect future transfusions by causing incompatibility. These antibodies may lead to acute or delayed hemolytic transfusion reactions and can also contribute to hemolytic disease of the fetus and newborn [1]. The Lewis blood group system is unique because its antigens are passively adsorbed onto red blood cells from plasma, leading to variable antigen expression [2]. Antibodies such as anti-Le^a and anti-Le^b are usually naturally occurring IgM antibodies that react at temperatures below 37 °C and are generally considered clinically insignificant [3]. Lewis antibodies can induce red cell agglutination and activate the complement cascade, leading to hemolysis. Importantly, they may demonstrate clinical significance even when they are not reactive at 37 °C. Notably, there is emerging evidence that anti-Lewis antibodies, although often considered clinically insignificant, can occasionally result in hemolytic transfusion reactions. The Rh blood grouping system is the second most clinically important blood system following the ABO group system. The major antigens of this blood grouping system, which include D, C, E, c, and e, are highly immunogenic and have the ability to induce HTR and HDFN [4]. Anti-E is a common, clinically significant Rh alloantibody frequently identified among alloimmunized patients across diverse populations and has been implicated in DHTR [5,6].

Case Presentation

Case 1

A 28-year-old female, gravida 3 para 1 living 1 (G3P1L1), presented with complaints of lower abdominal pain of one-day duration, with a history of a previous normal vaginal delivery two years prior and no prior history of blood transfusion. She was admitted and planned for normal vaginal delivery. Routine laboratory investigations revealed hemoglobin of 11.9 g/dL, total leukocyte count of 11,830 cells/mm^3, and platelet count of $3.40 \times 10^5/mm^3$. Blood grouping performed using column agglutination technology (CAT) identified her as O, RhD positive. In anticipation of obstetric blood loss, a requisition for one unit of packed red blood cells was received; however, major crossmatching of three units was found to be incompatible with agglutination strengths of 1+, 1+, and 3+ by CAT. Further immunohematological workup showed a positive direct antiglobulin test (DAT) with a negative autocontrol. Antibody screening using a three-cell panel demonstrated reactivity with Cell I (3+), Cell II (1+), and non-reactivity with Cell III, suggesting the presence of an unexpected alloantibody. Subsequent antibody identification using a 11-cell panel confirmed the specificity as an Anti-Le^b antibody. In view of the minimal intra operative blood loss,transfusion support was not indicated.

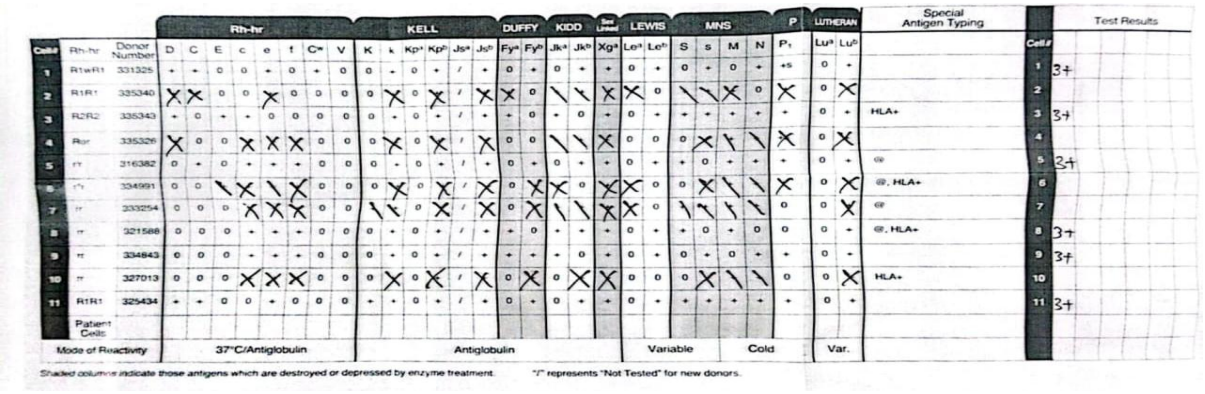

Figure 1. Antibody identification panel findings indicate presence of Anti-Le^b Antibody

Case 2

A 26-year-old primigravida at 37+3 weeks of gestation presented with complaints of reduced fetal movements for one day, with no associated comorbidities. Obstetric evaluation with ultrasonography and Doppler revealed a cerebroplacental ratio below the 5th percentile, suggestive of fetal hypoxia with a brain-sparing effect, necessitating emergency obstetric intervention. As part of preoperative preparation, one unit of PRBC was requisitioned for transfusion support. Initial crossmatching demonstrated compatibility with one unit. The patient had no prior history of blood transfusion. Immunohematological workup showed blood group B RhD negative, determined by column agglutination technology (CAT) Compatibility testing revealed one unit was crossmatched and compatible. Antibody screening performed using both CAT and manual gel card method demonstrated reactivity with Screening Cell I (2+), while Screening Cells II and III were non-reactive. Direct antiglobulin test (DAT) was negative, with a negative autocontrol, suggesting the presence of an alloantibody. Subsequent antibody identification using a panel revealed the presence of anti-Le^a antibody. Lower segment cesarean section (LSCS) was performed, delivering a baby with low Apgar score, with an estimated blood loss of 800 mL, for which one unit of PRBC was transfused and transfusion was completed uneventfully. Anti-Le^a antibodies generally do not affect transfusion outcomes, as they are usually naturally occurring IgM antibodies that react at cold temperatures and are rarely clinically significant.

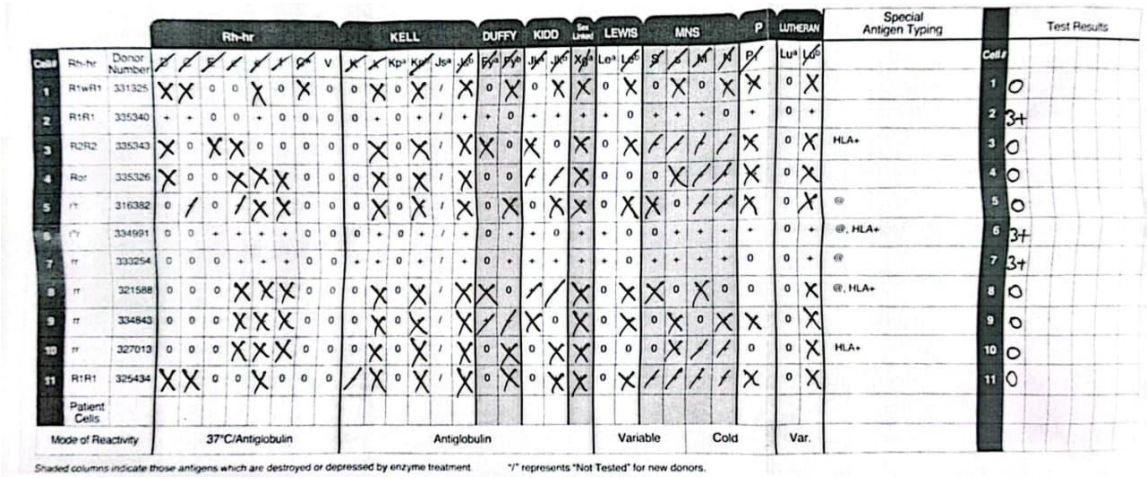

Figure 2. Antibody identification panel findings indicate presence of Anti-Le^a Antibody

Case 3

A 46-year-old female, with obstetric score of para 2 live 2, presented with complaints of amenorrhea for last 12 months, after which she developed heavy menstrual bleeding lasting 15-20 days associated with 4-5 fully soaked cloths per pad per day and previous history of 3 units of PRBC was transfused. Routine laboratory investigations revealed hemoglobin of 9.5 g/dL, total leukocyte count of 5060 cells/mm^3, and platelet count of 2.30 × 10^5/mm^3. Blood grouping performed using column agglutination technology (CAT) identified her as O RhD positive. In anticipation of potential perioperative blood loss, a requisition for one unit of packed red blood cells was received; however, major crossmatching of one unit was found to be compatible by both CAT and manual gel card methods. Further immunohematological workup showed a positive direct antiglobulin test (DAT) with a negative autocontrol. Antibody screening using a three-cell panel demonstrated reactivity with Cell I (0), Cell II (3+), Cell III (0), suggesting the presence of an unexpected alloantibody. Subsequent antibody identification using an 11-cell panel confirmed the specificity as anti-E (anti-E) antibody, one unit of PRBC was transfused and transfusion was completed uneventfully.

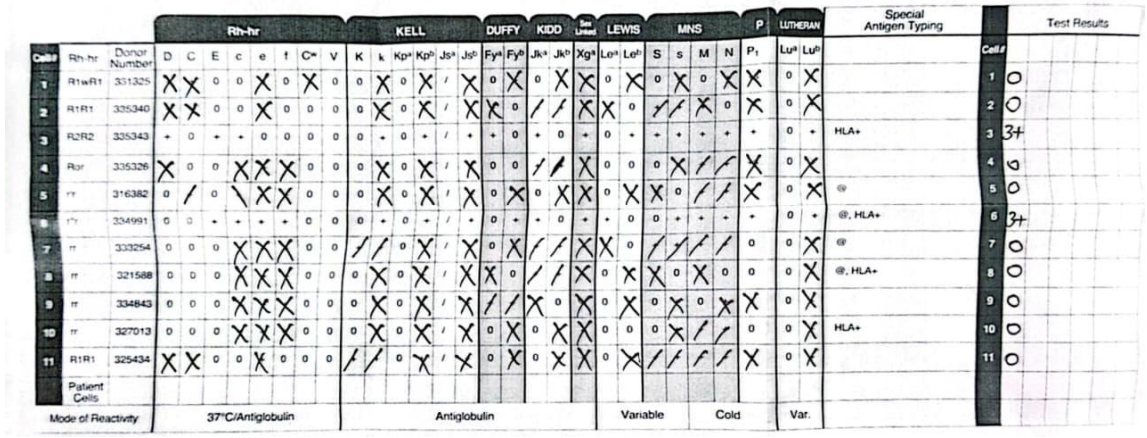

Figure 3. Antibody identification panel findings indicate presence of Anti-E Antibody

Discussion

Case 1

The Le-a and Lewis-b (Le-b) antigens are not expressed on RBCs and are adsorbed from plasma [6]. Generally, the clinically significant antibodies are those that agglutinate at 37 °C under in-vitro conditions and also during the IAT phase, usually classified as IgG antibodies. But the antibodies of the Lewis blood group system are normally considered to be naturally occurring and also fall into the IgM antibodies' classification [7]. Such antibodies usually agglutinate below 37 °C and are generally not considered to be clinically significant [8]. The antibodies of the Lewis blood group are commonly found in the serum of pregnant women and those having Le (a−b−) phenotype [9]. However, pregnancy-induced suppression of Lewis antigens may lead to a transient Le(a−b−) phenotype, predisposing to antibody formation. In the present case, crossmatch incompatibility with variable agglutination strengths [1+ to 3+] and a positive direct antiglobulin test (DAT) with negative autocontrol suggests alloimmune sensitization, likely pregnancy-related in the absence of prior transfusion. Similar observations have been reported by Mustafa et al. and Arthi et al., where Lewis antibodies were detected in patients without transfusion history, highlighting pregnancy as a potential immunizing factor [10]. Overall, in comparison with similar case reports, this case reinforces that while Lewis antibodies are usually benign, they can occasionally present with clinically relevant serological challenges, particularly in antenatal patients, warranting thorough immunohematological evaluation and selection of crossmatch-compatible blood units.

Case 2

Anti-Lewis antibodies are commonly seen in the serum of pregnant women and individuals possessing Le a− and Le b− antigens [9]. Among the various types of Lewis antibodies, is the most frequently encountered one. The most common form of Lewis antibodies, anti-Lea, anti-Le^a is often observed at room temperature, although it may react either with the indirect antiglobulin test or at 37 °C [8,9]. It is more common for anti-Le^a to cause acute HTR compared to anti-Le^b antibodies. Delayed HTR is another form of HTR that has been reported before [11]. In the present case, transfusion of crossmatch-compatible blood in a pregnant patient with anti-Lewis antibodies was uneventful. In contrast, Rajeswari et al. reported a delayed hemolytic reaction following transfusion of but crossmatch-incompatible blood in a similar setting. This highlights that Lewis antibodies are usually clinically insignificant but may cause hemolysis if incompatible units are transfused [6]. In the present case, transfusion of crossmatch-compatible blood in a patient with anti-Lewis antibody was uneventful, supporting their generally benign nature in transfusion practice. However, Lewis antigens are expressed on renal tissues and can induce cytotoxic immune responses. As reported by Spitalnik et al., Lewis-incompatible renal transplants may lead to graft rejection, indicating their potential clinical significance in transplantation settings [12].

Case 3

The present case, a multiparous woman with a history of prior transfusion, was found to have anti-E alloantibody. Despite the presence of this clinically significant antibody, transfusion was successfully completed using E antigen negative, crossmatch-compatible packed red blood cell units, with no evidence of hemolytic transfusion reaction. In contrast, Panja et al. reported a case of anti-E mediated delayed hemolytic transfusion reaction with acute kidney injury, despite initial compatibility, attributed to antigen exposure and an anamnestic immune response. Both cases showed DAT positivity, indicating in vivo sensitization; however, the difference in clinical outcomes highlights the critical importance of antigen-negative blood selection and comprehensive antibody screening in preventing transfusion-related complications [13].

Conclusion

In the present study, although Lewis antibodies (anti-Le^a and anti-Le^b) are generally considered clinically insignificant, their reactivity at room temperature and occasionally at 37 °C warrants careful consideration during pretransfusion testing. Provision of Le^a antigen-negative red blood cell units, crossmatched at 37 °C, may be beneficial in minimizing the risk of hemolytic transfusion reactions, particularly in cases demonstrating reactivity at body temperature. Thus, appropriate antibody identification and selection of antigen-negative, crossmatch-compatible units remain essential to ensure safe transfusion practices. This case highlights the clinical importance of detecting anti-E alloantibody during pretransfusion testing in a previously transfused multiparous patient. Despite crossmatch compatibility, the presence of a clinically significant Rh antibody underscores the limitation of compatibility testing alone. The likely transfusion of E antigen-negative red cell units contributed to the absence of any hemolytic transfusion reaction. Therefore, comprehensive antibody screening and identification, along with provision of antigen-negative, crossmatch-compatible blood, are essential to ensure safe transfusion and to prevent delayed hemolytic complications in sensitized individuals.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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References

1. Reid ME, Mohandas N. Red blood cell blood group antigens: structure and function. Semin Hematol. 2004;41(2):93–117. doi:10.1053/j.seminhematol.2004.01.001
2. Oriol R, Le Pendu J, Sparkes RS, Sparkes MC, Crist M, Gale RP, et al. Insights into the expression of ABH and Lewis antigens through human bone marrow transplantation. Am J Hum Genet. 1981;33(4):551–560.
3. Mollison PL, Engelfriet CP, Contreras M. Blood transfusion in clinical medicine. 10th ed. Oxford: Blackwell Science; 1997.

4. Daniels G. Human blood groups. 3rd ed. Oxford: John Wiley & Sons; 2013.
5. Xu P, Li Y, Yu H. Prevalence, specificity and risk of red blood cell alloantibodies among hospitalised Hubei Han Chinese patients. Blood Transfus. 2014;12(1):56–60. doi:10.2450/2013.0013-13
6. Al-Joudi F, Ali AB, Ramli MB, Ahmed S, Ismail M. Prevalence and specificities of red cell alloantibodies among blood recipients in the Malaysian state of Kelantan. Asian J Transfus Sci. 2011;5(1):42–45. doi:10.4103/0973-6247.75997
7. Makroo RN, Arora B, Bhatia A, Chowdhry M, Luka R. Clinical significance of antibody specificities to M, N and Lewis blood group system. Asian J Transfus Sci. 2014;8(2):96–99. doi:10.4103/0973-6247.137442
8. Mollison PL. The role of complement in the detection of blood group antibodies: special reference to the antiglobulin test. Transfusion. 1961;1(1):9–22. doi:10.1111/j.1537-2995.1961.tb00006.x
9. Gupta D, Gayathri A. Case series investigation on the Lewis system antibodies encountered during routine screening in a tertiary care hospital-based blood center. Asian J Transfus Sci. 2020;14(1):54–57. doi:10.4103/ajts.ajts_60_19
10. R A, V S, A HH, K SI, James S. Lewis-A antibody in clinical practice: a case report. Cureus. 2024;16(7):e64501. doi:10.7759/cureus.64501
11. Contreras M, Mollison PL. Delayed haemolytic transfusion reaction caused by anti-LebH antibody. Vox Sang. 1989;56(4):290. doi:10.1111/j.1423-0410.1989.tb02045.x
12. Spitalnik S, Pfaff W, Cowles J, Ireland JE, Scornik JC, Blumberg N. Correlation of humoral immunity to Lewis blood group antigens with renal transplant rejection. Transplantation. 1984;37(3):265–268. doi:10.1097/00007890-198403000-00010
13. Panja K, Upreti R. Delayed hemolytic transfusion reaction with acute kidney injury due to anti-E antibody in a 43-year-old woman with iron-deficiency anemia. Cureus. 2025;17(10):e93634. doi:10.7759/cureus.93634