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Anti-N Antibody Reacting at 37°C: An Unusual Reaction in Antibody Screening in a 20-Year-Old Male Liver Donor

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Authors' contributions

This work was carried out in collaboration between both authors. Authors MSA and MH contributed to the design, drafting and critical revision of the manuscript. Both authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Anti-N antibodies usually possess cold-reactive properties which make them clinically insignificant and are mostly classified as naturally occurring IgM antibodies. These antibodies sometimes trigger reactions at body temperature (37°C) or in the anti-human globulin phase resulting in serious medical outcomes such as delayed hemolytic transfusion reactions or hemolytic disease of the newborn. This case shows an extraordinary naturally occurring anti-N antibody which was detected in a 20-year-old male liver donor during standard antibody testing because of its unexpected reactivity at 37°C. The absence of any previous blood transfusions or medication use in the patient made this case stand out as particularly intriguing. The antibody identification was successful

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following the 'pre-warm' technique implementation while antigen phenotyping validated it as an IgG-type anti-N antibody. This medical case demonstrates the critical importance of recognizing unusual antibody responses during blood transfusions and organ transplants because uncommon reactions may lead to serious consequences.

Keywords: Anti-N antibody; MNS blood group system; transfusion medicine; serological testing; delayed hemolytic transfusion reactions.

1. INTRODUCTION

The MNS blood group system, discovered by Landsteiner and Levine in 1927, was the second to be identified after the ABO system. Among the antibodies in the MNS system, anti-M is a common "naturally occurring" antibody (Perrault, 1973). The S antigen was identified in 1947 by Walsh and Montgomery after the development of the antiglobulin test (Harmening, 2018). Most anti-M antibodies are cold-reactive and do not activate complement or react with enzyme-treated RBCs (Thakral et al., 2010). They are rarely associated with hemolytic transfusion reactions (Sancho et al., 1998).

Anti-N antibodies are less common than anti-M and are also typically naturally occurring, cold-reactive IgM or IgG agglutinins that do not activate complement or react with enzyme-treated RBCs (Perrault, 1973; Taj et al., 2025). They are clinically insignificant unless reactive at 37°C and have been linked to rare cases of mild hemolytic disease of the fetus and newborn (HDFN) (Ballas et al., 1985; Wiebe et al., 2024). Potent anti-N antibodies are more frequently found in individuals of African descent with a specific RBC phenotype (M+ N- S- s-) due to the absence of the N antigen (Harmening, 2018; Katagiri et al., 2024). Immune anti-N antibodies are extremely rare (Klein & Anstee, 2013). We report a case of naturally occurring anti-N that reacts at 37°C, identified during routine antibody identification testing (Kumawat et al., 2015).

2. CASE REPORT

A 20-year-old guy from Karachi, who's healthy and doesn't have any other medical issues, decided to donate a liver to his dad. His father had been struggling with chronic liver disease because of a hepatitis B infection, so they set up a liver transplant at Dow University of Health Sciences. This donor had never had a blood transfusion or taken any medication. For the usual pre-transplant checks, they sent a test request to Aga Khan University Hospital to identify any antibodies. The first blood tests came back showing a positive auto-control, which means his red blood cells reacted with his own serum at room temperature. But when they did a Direct Antiglobulin Test (DAT) with anti-IgG + C3d, it came back negative, ruling out any autoantibodies. They then checked three different antibody screening panels (ID-Diacell I-II-III, Biorad) and found positive reactions in all of them (2+, 3+, and 3+). They also noticed that the auto-control was positive right from the spin phase. So, they decided to run the antibody screening again using a method where they warmed everything up, and surprise! They got positive results across all three panels. To dig deeper, they used the Papain treatment method (ID-Diacell Papain Kit), which surprisingly turned up a negative result for the red cell antibody screening. But when they went ahead with the antibody identification using the warm technique, they found out he had an anti-N antibody using this 11-cell identification panel (ID-Diacell, Biorad). The reaction was pretty strong, 3+, with homozygous N+ N+ cells (Panels 4, 10, and 11) and negative with heterozygous M+ N+ cells (Panels 1, 3, 7, and 8), plus also negative with N-negative cells (Panels 2, 5, 6, and 9). They also checked other antigens for N, S, s, and M and found that he was M-, N-, S-, and s-. They treated his plasma with dithiothreitol, which confirmed there was an IgG-type anti-N antibody present. The antibody titer was 1:2. This report emphasizes a naturally occurring anti-N antibody that reacts at 37°C, which could actually be pretty important even though the donor hadn't had any blood transfusions before. It really brings home the need to check for these naturally happening antibodies during routine blood tests because their reactions at body temperature can affect transfusion practices.

3. DISCUSSION

Anti-N antibodies belong to the MNS blood group system and are usually naturally occurring and mainly cold-reactive IgM antibodies. These antibodies are often clinically insignificant unless they decide to react at 37°C or during the anti-human globulin (AHG) phase of testing. In this

case, we found the anti-N antibody in a 20-year-old male liver donor who had a serological profile showing an uncommon blood group discrepancy. While anti-N antibodies are generally more of a cold-reactive type and don't usually bind complement, if they do react at 37°C, that's when we start to worry about their clinical significance.

Normally, anti-N antibodies don't cause major issues, as they are linked to non-pathological clinical outcomes. They typically don't lead to hemolytic transfusion reactions (HTRs) or hemolytic disease of the fetus and newborn (HDFN) unless we see them react at body temperature (37°C), like in this instance (Perrault, 1973). A transfusion reaction is more likely if these antibodies show strong reactivity at 37°C, but that's pretty rare. When it happens, it can cause delayed hemolytic reactions, resulting in some transfusion-associated complications. Besides, while HDFN can be a concern in cases of maternal-fetal blood group incompatibility, instances of HDFN linked to anti-N are super rare (Harmening, 2018).

Interestingly, the IgM class of anti-N antibodies usually reacts in colder conditions and doesn't typically bind to complement or react with enzyme-treated red blood cells (RBCs). This is kind of similar to anti-M antibodies, which show the same cold-reactive behavior and limited clinical relevance, unless they react at body temperature (Thakral et al., 2010). However, in our case, the antibody was behaving unusually by reacting at 37°C, reminding us to stay on our toes about atypical antibody behaviors in blood donors, especially when we're talking about organ transplant recipients who might need careful crossmatching and serologic evaluations.

The phenotyping results were pretty noteworthy since the donor's red cell antigen profile showed the absence of the M, N, S, and s antigens, which are usually part of testing in the MNS blood group system. Plus, after treating with Dithiothreitol (DTT), we confirmed that the anti-N antibody was of the IgG nature, hinting that it could have some clinical significance in certain transfusion scenarios (Sancho et al., 1998).

Finding an anti-N antibody in a healthy individual with no prior blood transfusions is pretty unusual, given that naturally occurring antibodies in the MNS system are typically IgM types and don't usually trigger immune responses. The titer of 1:2 here suggests the anti-N antibody could definitely be clinically important at 37°C (Kumawat et al., 2015). This just goes to show how important it is to do a thorough antibody screening for blood donors; even naturally occurring antibodies might need our attention in a clinical setting.

4. CONCLUSION

In conclusion, this case really emphasizes the importance of rare blood group antibodies in organ transplantation and transfusion medicine. It's a reminder for clinicians and lab staff to keep an eye out for unusual antibody profiles, especially when there are discrepancies in routine serological testing. We need more studies and awareness about these antibodies to avoid adverse reactions in transfusions and organ transplant procedures.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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