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Can anti-A_1 cause hemolysis?

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An anti-A_1 was recently reported as cause of an acute hemolytic transfusion reaction,[1] adding to the list of sporadic anti-A_1 of supposed clinical consequence.[1] The proof requires the experimental confirmation of the antibody's exclusive specificity to the A_1 antigen, which remained difficult for many years, while the chemical basis for the A_1 and A_2 phenotypes had been controversial. The phenotypes have become more clearly identified with an A_2 individual being one whose red cells carry very few A type 4 antigens or lacks them completely.[2] Still, the antibody known as anti-A_1 remains less well defined, which *a priori* should be an antibody that binds the A type 4 antigen[2,3] and not simply an anti-A that reacts quantitatively in correlation with its potency.

The recent report[1] claiming hemolytic anti-A_1 in a patient with an A_2 phenotype was based on typing by the *Dolichos biflorus* lectin only – a modern routine serologic ABO reagent formulated to rapidly, but crudely, distinguish the A_1 and A_2 phenotypes solely by antigen levels. Also, IgM antibodies in the eluate post-transfusion reacted with A_2 cells, which is unexpected in a true A_2 individual. The authors[1] convincingly demonstrated the hemolysis to be caused by anti-A, but do not prove the causative antibody to be anti-A_1, on the basis of simple quantitative antibody reaction patterns with A_1 and A_2 cells.

Other equally feasible explanations, compatible with all data presented,[1] exist. For example, if this individual carries a para-Bombay phenotype (blood group A and secretor), expressing some A antigen, she could falsely type as A_2 with modern ABO reagents and, importantly, have anti-A in her plasma directed against the A type 2 antigen. This normal, prevalent form of anti-A is strongly hemolytic and would hence explain the acute, eventually fatal, hemolysis. Because of this and other alternative scenarios, studies like the recent report[1] must utilize genotyping to prove phenotypes and should ideally include biochemical data on antibody specificity to support their conclusions. The antibody could have been studied by glycomapping[4] to unequivocally determine its specificity: as an anti-A type 4, excluding

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cross-reactivity with the A type 2 antigen. The recent report's conclusions[1] may be correct. Its observations would corroborate the data by Jaben and colleagues who demonstrated elegantly[5] that an *A2* genotype-proven individual can make a hemolytic ABO antibody that reacts with A_1 cells, although they[5] did not define the precise specificity of the antibody.

Although red cells, polyclonal antibodies, lectins, and inhibitory substances defined the basis of most recognized blood group phenotypes, they are inadequate today to prove the fine specificity of antibodies and unequivocally define red cell antigens. Without clarity in defining the specificity of an antibody and its cognate antigen, doubts linger and the claimed conclusions may actually be inconclusive. We should be overly cautious with our conclusions in reports meant to influence transfusion policies and utilize the latest methodologies – enabling conclusions with less ambiguity.

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