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Anti-Emm, a rare specificity to the high-incidence antigen Emm in an Indian patient defining the new blood group system EMM (ISBT042)

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Abstract:

A transfusion recipient lacking a high-incidence antigen (HIA) and has corresponding alloantibody pose a problem in providing compatible blood unit. We encountered a patient with an antibody to an HIA that required identification to assess if compatible blood could be organized. A 65-year-old male was posted for coronary artery bypass grafting surgery. His blood specimen collected in EDTA was referred to the blood bank to provide blood for transfusion. The patient, grouped AB RhD+, had an antibody reacting in saline and antiglobulin phases. It agglutinated all the red blood cells (RBCs) of the 11-cell panel and random donors, indicating specificity to an HIA, though one of his siblings was compatible. After ruling out specificity to HIAs such as H, In^b, and INRA (IN5), the specimen was referred to the New York Blood Centre for further work-up. The antibody reacted with examples of red cells lacking HIA, except those with the Emm- phenotype. The patient's RBCs were typed as Emm-. Anti-Emm in the patient appeared to be naturally occurring as there was no history of transfusion. Naturally occurring alloantibody to an HIA, identified as anti-Emm in phenotype Emm-, is rare and the first of its kind to be reported from India. The case was instrumental in recognizing the Emm as the new blood group system assigned with the symbol ISBT042.

Keywords:

Emm, Emm- phenotype in Indian subject, high-incidence antigen, new blood group system

Introduction

There are over 376 blood group antigens recognized, most of which are classified into well-defined blood group systems on the basis of serologic, biochemical, and genetic consideration. Remaining others are currently unassigned to any blood group system and listed as collections (200 series), high incidence (901 series), and low incidence antigens (700 series).^[1] Emm (901008) is a high-incidence antigen (HIA) of the 901 series. As of now, 10 individuals with the

Emm- phenotype have been documented in the literature. All of them belonged to different nationalities with varied ethnic origin. The list includes (1) a Frenchman born in Madagascar, (2) a White African, (3) a Pakistani, (4 and 5) a French Canadian and their brother, (6 and 7) North African born in Madagascar and their sister, (8 and 9) two males from the USA, and (10) a patient from Japan.^[2-5] We report here two more examples from India, a patient and his brother, totaling 12 people with the rare Emm- phenotype in the world. Anti-Emm is regularly present in Emm- subjects as a naturally occurring antibody and may

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give direct agglutination of RBCs suspended in the low ionic strength solution (LISS), but stronger reactivity is often seen by the indirect antiglobulin test (IAT). There has been no report of hemolytic disease of the fetus and newborn (HDFN) due to anti-Emm, though a single case with an acute hemolytic transfusion reaction was recorded, reflecting its clinical significance.^[5] We encountered an antibody to an HIA posing a problem in finding compatible blood for a patient. The antibody specificity was determined as anti-Emm. This case the first example of anti-Emm found in the Gujarati community from India.

Case Report

A 65-year-old male posted for coronary artery bypass grafting. The patient's blood specimen was collected in EDTA and used in serological and molecular studies. The reagent antisera used for forward blood grouping were from commercial source (Tulip, Goa, India), and the red blood cells (RBCs) used for reverse grouping, cross-matching, antibody detection, and identification tests were made available from local sources. The serological tests were performed by tube techniques using RBCs suspension of 3%–4% concentration in LISS in saline phase as well as in IAT phase. The tests were incubated for 15 min, separately at 22°C in saline phase for direct agglutination and at 37°C for IAT phase following which results were read after centrifugation. The blood samples obtained from his family members were also tested in the same manner. The antibody was tested with the RBCs lacking rare HIA preserved at New York Blood Center (NYBC) using a similar serological approach.

Genomic DNA was isolated by standard methods from peripheral blood (QIAamp, QIAGEN, Inc., Valencia, CA, USA) of the proband and his family members. Whole-genome sequencing by PCR-free Illumina paired-end short reads of the proband and his Emm-brother was performed. The *PIGG* exon 12, including the flanking intron regions, was amplified and sequenced by Sanger method. Sanger sequences were aligned to reference (NM_001127178.3) with ClustalX and analyzed. The patient and his family members endorsed their consent for the study on their blood.

The patient was typed as A₁B RhD⁺. The antibody screen test was positive, and in the face of negative findings on auto-control test (patient's RBCs + patient's plasma) and the DAT, the antibody was specified as an alloantibody. The antibody reacted equally well with the random donors' untreated RBCs and those treated with enzymes papain and trypsin as well as chemicals, dithiothreitol and 2-aminoethylisothiuronium bromide. The antibody reacted stronger in IAT phase.

The alloantibody reacted in equal strength with all red cells in the 11-cell panel and with RBCs of a large number of random donors, indicating its specificity toward some HIA. The antibody was compatible with the RBCs of his younger brother. The specificity to HIAs that were previously found in India, e.g., H, In^b, Co3, and IN5 (INRA), was ruled out by testing the antibody with RBCs lacking these antigens.

The patient's blood specimen was referred to NYBC for further work-up. The antibody specificity was identified as anti-Emm by testing with known Emm- RBCs from the in-house collection. No other antibodies were detected in the patient's plasma using Emm- RBCs or by testing the patient's plasma (absorbed 3 times to remove the anti-Emm) by PEG IAT.

The patient's red cells were typed for the other blood groups by serological and or genomic methods as follows:

C+E-c+e+V-VS-; M+N+S+s+U+;K-k+Kp(a-b+) Js(a-b+); Fy(a+b+); Jk(a+b-); Lu(a-b+); Di(a-b+); Co(a+b-); Do(a-b+) Hy+Jo(a+); LW(a+b-); Sc1+Sc2-; P1+; Le(a-b+); Emm-.

In the whole genome analysis, over 5000 homozygous genetic variants were identified in the proband and his brother. Those with a frequency of <0.001 in the world wide genome databases would be potentially the cause of the rare phenotype. After filtering to those with frequency of <0.001, only one rare variant remained, a 2-base pair (bp) deletion in the *PIGG* gene that results in a frame-shift and premature stop codon (NM_001127178.3:C.2624_2625delTA, p.Leu875*, rs771819481). Sanger sequencing of *PIGG* exon 12 confirmed the 2-bp deletion in the proband and his brother, heterozygosity in the children, and absence in his wife.

Discussion

Persons lacking HIA are rare, and if the alloantibody to the corresponding antigen is present, they pose problem in finding compatible blood for transfusion. That is the problem we faced for a patient in finding compatible blood among our pool of donors. Cross-match testing of RBCs from siblings with the patient's antibody may find compatibility should any of them harbor the same trait. One brother was found compatible and kept on standby to meet emergency requirement. However, it was important to identify the specificity of the antibody so as to organize more blood units as there was a clear need of transfusions through surgical treatment. The centers that maintain a rare donor registry could help. While there are a few rare blood groups encountered in India,^[6] the exhaustive rare donor registry is not

in place for the moment. So also, there is no frozen blood program exists in India. Besides, there is no availability of the extensively typed rare red cell panels at the references centers where one can refer such cases for investigation. With these prevailing limitations, the alloantibody to HIA in the present case posed a tremendous difficulty to identify the antibody involved on the one hand and as to procure an appropriate blood unit for transfusion on the other. International collaboration may serve useful purpose in such circumstances.

Like in other Emm- individuals, the antibody in the present case was identified as naturally occurring anti-Emm with no history of transfusion.^[2-5] The clinical significance of this antibody remains obscure as only one case with anti-Emm reported from Japan experienced an acute hemolytic reaction to incompatible blood transfusions.^[5] There is no information regarding its involvement as the cause for HDFN as most of the reported individuals with anti-Emm were found in nontransfused males. As was found in previous examples, anti-Emm in the present case was IgG in nature.

As was the case with previously reported examples, anti-Emm in our patient gave direct agglutination of RBCs at room temperature in LISS, with optimal reactivity being in antiglobulin phase at 37°C. Likewise, consistent with other examples, anti-Emm in the present case reacted well with RBCs pretreated with proteolytic enzymes or chemicals that cleaved sulfhydryl group on the cell membrane. It had earlier been reported that the Emm antigen is carried on a glycosyl phosphatidylinositol-linked protein in the RBC membrane.^[7]

The antibody specificity was determined to be anti-Emm, revealing the first example of its kind in the family belong

to Gujarati Indian population. The molecular study carried out on present case defined the *gene* responsible for inheritance of the Emm antigen.^[8] The data were deliberated at the meeting of the ISBT Working Party on Immunogenetics and blood group terminology held on December 10, 2020. The Emm received a status of a new blood group system and was assigned the numerical system number EMM042.

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Conflicts of interest

There are no conflicts of interest.

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