Analysis of anti-M antibody status and blood transfusion strategy in Hunan, China

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Background: By analyzing the detection rate of anti-M antibody in patients with the MNS blood group system in the Hunan area, we aimed to explore its clinical significance and blood transfusion strategy.

Methods: We retrospectively analyzed the clinical data of patients who had been confirmed to contain anti-M antibodies through serological methods such as the saline tube method and cassette anti-human globulin method.

Results: Irregular antibody screening tests had been applied to 94,452 patients, from which 652 results were positive. Among those positive patients, 93 cases were positive for anti-M antibodies, accounting for 14.26% of the positive rate of irregular antibodies; 11 cases had a blood transfusion history, accounting for 11.8%; 59 cases had a pregnancy history, accounting for 63.4%; and 2 cases had a transplant history, accounting for 2.2%. The patients with anti-M antibodies included 23 pregnant woman, accounting for 24.7%, and 19 tumor patients, accounting for 20.4%. A total of 66 cases were immunoglobulin M (IgM) + immunoglobulin G (IgG) class, accounting for 71.0%, 26 cases were IgM class, accounting for 28.0%, and 1 case was IgG class, accounting for 1.0%.

Conclusions: The detection rates of anti-M antibody in the Hunan area and unexpected antibodies in literature reports are mainly related to a pregnancy history, and the type of antibody is predominantly IgM + IgG class. The clinical significance of anti-M antibody cannot be ignored, and three media should be used for cross-matching of blood wherever possible to ensure the safety of blood transfusion.

Keywords: MNS blood group system; anti-M antibody; blood transfusion strategy

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Introduction

Naturally occurring anti-A and anti-B are the only red cell antibodies commonly found in human serum or plasma. All other antibodies are called “unexpected red cell antibodies” (1). The existence of unexpected antibodies will cause many adverse blood transfusion reactions in patients who receive normal blood transfusion treatment, such as fever, chills and other symptoms in mild cases, and hemolytic blood transfusion reactions in severe cases, which are a serious threat to the life and health of patients (2,3).

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Antibody detection plays a crucial role in blood transfusion medicine because it can detect irregular or unexpected antibodies, and unexpected antibody positivity is an important cause of hemolytic transfusion reactions.

The MNS blood group system was discovered in 1927. It was the second blood group system discovered, and its complexity is second only to that of the Rh system (4). Anti-M is a naturally occurring antibody of the MNS blood group system. This antibody is the most reactive at temperatures below 37 ℃, has an optimum temperature of 4 ℃, and is considered clinically insignificant (5). In this study, anti-M antibodies were mainly immunoglobulin M (IgM) + immunoglobulin G (IgG) class, the clinical significance of anti-M antibody cannot be ignored, and three media should be used for cross-matching of blood wherever possible to ensure the safety of blood transfusion. We present the following article in accordance with the MDAR reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4999/rc).

Methods

Specimen origin

A total of 93 patients with anti-M antibody positive results from January 2018 to November 2021 in The Third Xiangya Hospital of Central South University were selected for analysis. Blood samples were collected and performed routine blood group serological examination with the assignment of the informed consent of patient. This study is a retrospective analysis, which may lead to bias in the results. We are about to start further confirmation in a multicenter clinical laboratory. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All reviewed procedures were approved by the Medical Ethics Committee of The Third Xiangya Hospital of Central South University (No. 2021-S307).

Experimental reagents

Monoclonal anti-A antibody and anti-B antibody (Beijing Jinhao Pharmaceutical Co., Ltd., Beijing, China; batch number 20211000704), anti-D (Shanghai Blood Biomedicine Co., Ltd., Shanghai, China; batch number 20210501), monoclonal anti-M antibody (Shanghai Blood Biomedicine Co., Ltd.; batch number 20210128), human ABO reverse typing reagent (Jiangsu Libo Pharmaceutical Biotechnology Co., Ltd., Nanjing, China; batch number 202110018), anti-human globulin microcolumn gel card (Changchun Boxun Biological Technology Co., Ltd., Changchun, China; batch number 20210801), Rh classification card (Changchun Boxun Biological Technology Co., Ltd.; batch number 20210901), unexpected antibody screening cells (Jiangsu Zhongji Wantai Biopharmaceutical Co., Ltd., Wuxi, China; batch number 20210104), 0.1 M of hydrochloric acid solution, and dithiothreitol (DTT; Nanjing Dulai Biological Technology Co., Ltd., Nanjing, China; C0075).

Experimental instrument

Dedicated incubator (Changchun Boyan Scientific Instruments Co., Ltd.; model: FXQ), medical centrifuge (Changchun Boyan Scientific Instruments Co., Ltd.; model: TD-A), and washing cytocentrifuge (Kubota, Tokyo, Japan; model: KA-2200).

Statistical analysis

Statistical analysis was performed using the software SPSS 23.0 (IBM Corp., Armonk, NY, USA) and the *t*-test was used to compare all measurement data. When $P<0.05$, the difference was considered statistically significant.

Results

Specificity and sex distribution of anti-M antibodies

Among the 652 cases of unexpected antibody positive patients, 93 cases were anti-M antibody positive, accounting for 14.26% of accidental antibody positivity. Among those 93 cases, 71.0% were females, and 29.0% were males, making the anti-M positivity rate of females significantly higher than that of males. The combination of IgM + IgG properties accounted for 71.0%, IgM properties accounted for 28.0%, and IgG properties accounted for 1.0%. Among anti-M antibodies, IgM + IgG properties accounted for the highest proportion, and there was a statistically significant difference between IgM + IgG properties and IgM properties ($P<0.05$), but IgG properties were not statistically significant due to the small number. Patients with a pregnancy history accounted for 62.4%, those with no pregnancy history accounted for 37.6%, so the positive detection rate with pregnancy history was relatively high. Cases with no history of blood transfusion accounted for 88.2%, and the difference was statistically significant

Table 1 Anti-M antibody specificity and gender distribution

Age (years)	Gender	Antibody property, n			Pregnancy, n		Transfusion, n		Transplantation, n	
		IgM	IgM + IgG	IgG	Yes	No	Yes	No	Yes	No
0–20	M	2	2	0	0	4	0	4	0	4
	F	2	3	0	0	5	0	5	0	5
21–40	M	0	2	0	0	2	0	2	1	1
	F	6	26	1	30	3	1	32	0	33
41–60	M	2	9	0	0	11	6	6	0	11
	F	7	11	0	18	0	0	17	1	18
61–80	M	6	2	0	0	8	1	7	0	8
	F	1	8	0	9	0	2	7	0	9
t		5.975	14.966	1.000	–	–	3.513	–	1.422	–
P		<0.001	<0.001	0.320	–	–	0.001	–	0.158	–
Total		28.0%	71.0%	1.1%	62.4%	37.6%	11.8%	88.2%	2.2%	82.8%

IgM, immunoglobulin M; IgG, immunoglobulin G; M, male; F, female.

(P<0.05). Cases with a history of transplantation accounted for 2.2%, and those with a history of no transplantation accounted for 82.8%. Since the number of patients with a transplantation history was small, there was no statistical significance (*Table 1*).

Disease distribution of 93 patients with anti-M antibody positive

Among the disease distribution of 93 cases of anti-M antibodies, pregnant women comprised the largest proportion of 23 cases, accounting for 24.7%. Anti-M antibodies were the second most common non-RhD antibody found in pregnant women, with approximately 25% of the population lacking the M-antigen and hence capable of producing anti-M antibodies when exposed to the antigen (6,7). Antigens such as MNS are expressed on erythroid progenitor cells, and anti-M/anti-N can destroy erythroid progenitors, and the hemolysis rate is fast, causing fetal edema, anemia, and abortion (8). Given the abundance of sialic acids on glycophorin A, on which MN antigens are present, some infected hosts may evoke so-called naturally occurring, or microbiota cross-reactivity anti-M during immune response to invading pathogens, thus there is some association between microbial infection and red blood cell (RBC) alloimmunization (9). As mentioned above, there were 19 tumor patients (including cervical cancer, renal cancer, ovarian cancer, colon cancer, leukemia, etc.), accounting for 21.5%; 11 cases of orthopedic diseases (including femoral head necrosis, vertebral bone destruction, lumbar disc herniation, etc.), accounting for 11.8%; gynecological diseases (such as hysteromyoma, adenomyosis, ovarian cyst, etc.) and urinary diseases (renal insufficiency, uremia, congenital stricture of ureter, etc.) in 9 cases each, accounting for 19.4%; and digestive diseases (gastrointestinal bleeding, liver cirrhosis, etc.) in 8 cases, comprising 8.6%. There were 2 cases of renal allograft, comprising 2.2%, and 12 cases of other diseases (such as congenital heart disease, tonsillitis, pulmonary infection, etc.), accounting for 12.9%. The differences were statistically significant (P<0.05) (*Table 2*).

Indirect anti-human globulin test titer in 10 pregnant women

Hemolytic disease of the fetus and newborn (HDFN) belongs to a class of homopassive immune hemolytic disease, which is caused by the presence of irregular IgG antibodies in the mother that do not conform to fetal erythrocytes (10). Therefore, prenatal immunization intervention is helpful to reduce the incidence of neonatal hemolytic disease, and prenatal screening of irregular antibodies and determination of antibody titer are the basis and premise for effective intervention (11). In this study,

Table 2 Disease distribution of 93 patients with anti-M antibody positivity

Disease/condition classification	Example number	Proportion (%)	t	P value
Pregnant women	23	24.7	5.498	<0.001
Tumor patients (such as cervical cancer, renal cancer, ovarian cancer, colon cancer, leukemia, etc.)	19	21.5	4.860	<0.001
Orthopedic diseases (such as femoral head necrosis, vertebral bone destruction, lumbar disc herniation, etc.)	11	11.8	3.153	0.001
Gynecological diseases (such as hysteromyoma, adenomyosis, ovarian cyst, etc.)	9	9.7	3.140	0.002
Urinary diseases (renal insufficiency, uremia, congenital stricture of ureter, etc.)	9	9.7	3.513	0.002
Digestive diseases (gastrointestinal bleeding, liver cirrhosis, etc.)	8	8.6	2.943	0.004
Renal allograft	2	2.2	1.422	0.022
Other diseases (such as congenital heart disease, tonsillitis, pulmonary infection, etc.)	12	12.9	3.692	<0.001

Table 3 Titers of indirect anti-human globulin test in 10 pregnant women

Pregnant woman	IAT titer	Prenatal titer	Perinatal valence	DAT	Fetal M antigen status
Pregnant woman 1	1:2	1:2	1:2	–	NN
Pregnant woman 2	1:4	1:4	1:8	–	NN
Pregnant woman 3	1:2	1:2	1:2	–	NN
Pregnant woman 4	1:2	1:2	1:4	–	MN
Pregnant woman 5	1:4	1:4	1:4	–	MN
Pregnant woman 6	1:16	1:16	1:32	+	MN
Pregnant woman 7	1:4	1:4	1:4	–	MN
Pregnant woman 8	1:2	1:2	1:2	–	NN
Pregnant woman 9	1:8	1:8	1:8	–	NN
Pregnant woman 10	1:4	1:4	1:4	–	NN

IAT, indirect antiglobulin test; DAT, direct antiglobulin test; NN, fetal NN antigen status; MN, fetal MN antigen status.

there were 1 case of M antigen positive and 6 cases of M antigen negative fetuses, and the maternal antibody titer was unchanged. There were 3 M antigen positive fetuses with elevated maternal antibody titers (*Table 3*).

RBC transfusion therapy and blood transfusion assessment

When IgM anti-M antibodies are present but not reactive at 37 ℃, the selection of transfusion RBC units are matched or compatible with patients' ABO and RhD. However, M antigen-negative RBC are necessary for transfusion when the antibody is reactive at 37 ℃ or is of IgM + IgG class. Infusion effect: after 24 hours of transfusion of 2 units of M antigen-negative RBC, hemoglobin (Hb) increased by 10 g/L, which was considered effective (12) (*Table 4*).

Discussion

MNS is a highly polymorphic blood group comprising 50 antigens recognized by International Society of Blood Transfusion by June 2021, some of which may have been generated by genomic recombination among the closely

Table 4 Evaluation of therapeutic effect after transfusion of 2 units of M antigen-negative RBC in 10 patients with anti-M antibody positive

Patient	Pre-transfusion Hb (g/L)	Hb 24 hours post-transfusion (g/L)	Hb 24 hours elevation of post-transfusion (g/L)	Infusion effect	Transfusion reaction
Patient 1 (IgM)	45.3	55.4	10.1	Effective infusion	None
Patient 2 (IgM)	40.5	51.2	10.7	Effective infusion	None
Patient 3 (IgM)	39.4	50.3	10.9	Effective infusion	None
Patient 4 (IgM)	38.6	49.6	11.0	Effective infusion	None
Patient 5 (IgM)	42.8	52.9	10.1	Effective infusion	None
Patient 6 (IgM + IgG)	35.6	48.8	13.2	Effective infusion	None
Patient 7 (IgM + IgG)	44.6	55.1	10.5	Effective infusion	None
Patient 8 (IgM + IgG)	55.0	66.0	11.0	Effective infusion	None
Patient 9 (IgM + IgG)	53.1	64.5	11.4	Effective infusion	None
Patient 10 (IgM + IgG)	46.2	57.0	10.8	Effective infusion	None

RBC, red blood cell; Hb, hemoglobin; IgM, immunoglobulin M; IgG, immunoglobulin G.

linked genes *GYPA*, *GYPB*, and *GYPE* (13). In the blood group system of MNS, anti-M antibody is the most common accidental antibody, and immune stimulation is an important factor for the generation of anti-M antibody. The generation of anti-M antibody is mostly due to blood transfusion history or pregnancy history, which is not regular and will not constantly appear in the serum without corresponding antigen. It can cause ABO incompatibility, cross match incompatibility, hemolytic blood transfusion reaction, HDFN, etc. (14,15).

Production of the antibodies is caused by diversity of antigens and immunity between maternal and fetal immunity, blood transfusion, and transplantation and immune and hematological diseases (16). An accidental antibody is an immune response against a foreign erythrocyte antigen; anti-M antibody is a common accidental antibody in pregnant women, which can cause HDFN (17). For neonatal hemolytic diseases with negative direct antiglobulin test (DAT), since MNS and other antigens are expressed on erythroid progenitor cells and anti-M destroys erythroid progenitor cells rather than mature RBCs, the hemolysis related tests may be negative even though the anemia is severe at birth. There may be no typical changes in neonatal free interferers, direct anti-human globulin tests and diffusion tests, and the bilirubin level may not increase significantly. At this time, early and effective treatment should be actively carried out in combination with the results of maternal antibody identification, neonatal birth score and Hb level. If the proportion of severe anemia and jaundice of HDFN caused by IgG anti-M in neonates is high, it will not only lead to acute death of neonates, but also lead to the occurrence of bilirubin encephalopathy. Therefore, IgG anti-M detection is essential. A study has found that the incidence of anti-M-induced severe HDFN is extremely low (18). Anti-M antibodies in humans are divided into natural antibodies and immune antibodies, including the more common IgM properties, IgM + IgG properties, or IgG properties alone, however IgG antibodies are relatively rare (19). In this study, 93 cases of anti-M antibody positive patients had a history of pregnancy, which was the highest detection rate group, accounting for 62.4%. The detection rate of IgM + IgG properties was the highest, accounting for 71.0%; IgM properties were the second highest, accounting for 28.0%. Anti-M may be naturally occurring or immune mediated due to exposure in a previous pregnancy, transfusion, or transplantation (6). It has been found that the positive rate of accidental antibody detection in the serum of female blood donors with more than 3 previous pregnancies was higher than the titer of IgG anti-M antibody, which suggested that the positive rate of accidental antibody in the plasma of female blood donors may vary with the number of pregnancies. This may be because in the first pregnancy, the B cells in the lymphocyte subsets in the mother undergo repeated immune stimulation by antigens to activate and proliferate to produce plasma cells and memory B cells. When pregnant again, memory B cells are re-stimulated by the same antigen and then rapidly activated to produce a

large number of specific and unexpected antibodies (20).

Accidental antibodies are other antibodies in the blood that are important to the body, but in pregnant women can cause hemolysis in the newborn. As a result of the placental barrier can effectively stop the IgM irregular antibodies into the fetus, and irregular antibody IgG class once through the placental barrier into the fetal blood circulation, can quickly destroy fetal RBCs in the body, make the RBCs to shorten the life, children can appear due to hypoalbuminemia anasarca, can appear outside the medullary hematopoiesis, jaundice. Hyperbilirubinemia crosses the blood-brain barrier and leads to bilirubin encephalopathy, resulting in lifelong disability and other irreversible damage (21). In this study, there were 1 case of M antigen positive and 6 cases of M antigen negative fetuses, and the maternal antibody titer was unchanged. There were 3 cases of M antigen positive fetuses, the maternal antibody titer increased, the titer was less than 1:64. If the maternal antibody titer ≥1:64, pregnant women should receive intervention according to the specific situation, including propyl ball therapy, phototherapy, hormone therapy, and exchange transfusion therapy (22). Although anti-M antibodies rarely cause hemolytic disease in neonates, anti-M antibodies are detected in pregnant women who should be retested for anti-M antibody titers at 28 weeks of gestation. If the titer of anti-M antibody in pregnant women is ≥1:16 or in the second pregnancy, the antibody titer should be tested every 4 weeks. Intervention for pregnant women with abnormal antibody titer can significantly reduce the incidence of neonatal hemolytic disease, prolong the time of neonatal jaundice, and reduce the severity of jaundice. Therefore, prenatal determination of maternal antibody titer can assist in determining the risk of neonatal hemolytic disease after birth. If anti-M antibody positive pregnant women find IgG components and abnormal maternal antibody titer during pregnancy, the MN phenotype of parents and fetus should be determined, and the mother should undergo continuous prenatal serological monitoring. To prevent the fetus from developing severe HDFN.

In this study, tumor patients accounted for 20.4%, orthopedic diseases accounted for 11.8%, gynecological diseases and urinary diseases accounted for 9.7%, digestive diseases accounted for 8.6%, and other diseases accounted for 12.9%. It has been reported in relevant literature that history of blood transfusion, digestive system disease, chronic kidney disease, solid tumor and hematological disease, and severe medical disease are independent risk factors for irregular antibody detection (23,24).

It has been found (25) that in transplanted patients, if the anti-M antibody was naturally occurring, Identifying antibodies in a mixture of IgM and IgG antibodies. As the antibody was reactive at 37 ℃ and showing incompatibility during cross-matching, the antibody should be considered as potentially clinically significant. In this study, the anti-M-antibody was detected in 2 transplant patients. Close attention should be paid to the antibody status of patients requiring a blood transfusion, and they should be screened regularly for unexpected antibodies.

Most of the anti-M and anti-N were inactive at 37 ℃, which is of little clinical significance. The effects of these 2 antibodies are usually not considered in clinical blood transfusion. Antigen-negative or indirect antiglobulin test (IAT) compatible RBCs should be transfused for recipients with M or N antibodies active at 37 ℃. In this study, when IgM anti-M antibodies were present, but not reactive, at 37 ℃, the selection of transfusion RBC units were matched or compatible with patients' ABO and RhD. However, M antigen-negative RBCs are necessary for transfusion when the antibody is reactive at 37 ℃ or is of IgM + IgG class. This transfusion strategy achieved the expected effect on Hb level, and the transfusion treatment achieved satisfactory results.

In conclusion, the detection rate of anti-M antibody in Hunan is mainly related to the pregnancy history, with IgM + IgG type as the main class, which is a relatively common accidental antibody. In recent years, it has been reported in some Southeast Asian countries, Suzhou and Henan, and anti-M antibody is a relatively common accidental antibody. The type of anti-M antibody is mainly IgM in Southeast Asia and Henan, while the type of anti-M antibody is mainly IgG in Suzhou (4,17,26). Attention should be paid to the detection of anti-M antibodies in normal work. Most anti-M antibodies are temperature-responsive, the strongest reaction at 4 ℃, a weak reaction at room temperature, and a weak or even no reaction at 37 ℃, which easily results in missed detection. Therefore, the test tube technique and microcolumn gel technique should be carried out at different temperatures during antibody identification, and DTT and 0.2 N hydrochloric acid can also be used to improve the detection rate of anti-M antibodies. For patients with anti-M-specific antibody, the saline technique, polyamine technique, and microcolumn gel technique should be used in cross-matching whenever possible, and M-negative RBC components of blood donors should be screened for transfusion, so as to avoid false negative results of cross-matching caused by M heterozygous antigen of

blood donors and ensure safe blood transfusion. For patients with anti-M antibodies, screening of unexpected antibodies should be carried out regularly after blood transfusion, so as to minimize the damage of antibody-mediated transfusion of RBCs, thus avoiding hemolytic transfusion reaction and ensuring the safety of blood transfusion of patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All reviewed procedures were approved by the Medical Ethics Committee of The Third Xiangya Hospital of Central South University (No. 2021-S307). Blood samples were collected and performed routine blood group serological examination with the assignment of the informed consent of patient.

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