Case Report

Case report of anti JMH: A high-titer, low-avidity antibody posing difficulty in immunohematological tests

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ABSTRACT

This report presents a patient with anti-John Milton Hagen (JMH) posing difficulties in the immunohematological test in the Blood Bank Unit of Universiti Kebangsaan Malaysia Medical Center. A 1-year-8-month-old boy was referred to our center to rule out acute leukemia from a private hospital. A crossmatch request was sent to the Blood Bank before the bone marrow biopsy. Our testing revealed his blood grouping as O Rh-D positive. His Direct Antiglobulin Test was positive, and his antibody screening and antibody identification showed weak pan-reactivity. However, reactions were negative with enzyme-treated cells. Red cell elution showed interestingly no reaction in the eluate, suspected to be due to drug-induced autoantibody. Further tests of antibody titration and neutralization test suggest it could be a high-titer low avidity (HTLA) antibody, most likely Anti-JMH. Although HTLA antibodies are clinically insignificant, they can cause confusion and delay in issuance of blood products. There are also cases of clinically significant HTLA antibodies. Determining the type of HTLA antibody may guide the extent of further testing required to utilize resources best and, most importantly, to assure patient safety.

Key words: Anti-John Milton Hagen, High-titer low avidity antibody, Neutralization test, Pan-agglutination, Titration method

Anti-John Milton Hagen (JMH) antibody produced against high-frequency red cell antigen JMH is a high-titer and low avidity (HTLA) antibody [1]. The HTLA antibodies include anti-Chido (anti-Ch), anti-Rodgers (anti-Rg), anti-Cost-Stirling (anti-Cs^a), anti-York (anti-Yk^a), anti-Knops (anti-Kn^a), anti-McCoy (anti-McCa), and anti-JMH) [2]. These antibodies are usually immunoglobulin G (IgG) type, non-complement binding, and do not cause hemolysis [3]. They usually show weak reactions at the anti-human globulin (AHG) phase of the indirect antiglobulin test (IAT) and pose difficulties in serological testing, such as interference with the identification of underlying concomitant clinically significant alloantibody [4]. Therefore, it is necessary to remove these antibodies to determine the underlying alloantibodies, if any [2]. The majority of the HTLA antibodies are not clinically significant. The titration method is helpful in confirming the presence of HTLA antibodies. Still, interference in serological testing poses a challenge and causes a delay in the supply of blood to the patient [3]. JMH is usually a clinically benign antibody, but cases of hemolytic transfusion reactions have been reported [5]. Their presence mostly complicates the immunohematological test such as antibody identification, resulting in a delay in the patient's transfusion per se [3].

Here, we report the case of a boy having developed anti-JMH that posed difficulty in resolving antibody identification. This case report may help in the dissemination of knowledge in the resolution of HTLA antibody cases especially when it interferes with immunohematological tests.

CASE REPORT

A 1-year-8-month-old boy diagnosed neonatally with Down Syndrome and congenital hypothyroidism with a history of Transient Abnormal Myelopoiesis, was referred to our Center for suspicion of acute leukemia along with acute respiratory distress syndrome from a private hospital in Malaysia. He was treated with multiple antibiotics due to severe infection before he was referred. The patient has a recent history of blood transfusion from a previous hospital 2 weeks before.

On arrival at our center, the patient was afebrile, and vital signs were stable. The patient has hepatomegaly, otherwise, no

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bleeding tendencies, lymphadenopathies, splenomegaly, or other remarkable findings.

The patient's hemoglobin was 10.2 g/dL, white blood cell was 24.1×10^9/L, and platelets were 914×10^9/L. Full blood picture showed a mild normochromic normocytic anemia with 43% blasts which were moderate to large, high nuclear to cytoplasmic ratio, round nuclei, open chromatin, prominent nucleoli, basophilic cytoplasm with no Auer rods. Bone marrow and trephine (BMAT) biopsy findings are consistent with Acute Myeloid Leukemia (AML). Other laboratory investigations, such as renal profile, serum electrolytes, liver function test, and iron profiles, were normal.

A request for cross-matched blood was sent to the Blood Bank before the BMAT procedure. The blood group was O RhD positive, confirmed using a column agglutination test (CAT) (DiaMed, Cressier, Switzerland). The probable Rh genotype was R1R1 (CDe/CDe) performed using the CAT (DiaMed, Cressier, Switzerland). Direct AHG test (DAT) with polyspecific AHG and monospecific anti-IgG using the "ID-Card "LISS/Coombs" showed a positive result (2+) with negative anti-C3d. Further, the red cell elution test using the acid citrate method showed no reaction in the eluate. Considering 2+ reaction with the DAT and the severe infection with multiple antibiotics administration history, a drug-associated antibody was suspected to cause positive DAT.

The antibody screening with three cell panels (Bio-Rad ID-DiaCell I-II-III Asia) and antibody identification test with 11 cell panels (Bio-Rad ID DiaPanel, ID DiaPanel-P,) using manual method by CAT showed a weak (1+) pan-agglutination reaction. However, the reaction was destroyed with papain. Antibody identification was continued using the tube method, performed by Phenocell (bioCSL Phenocell™ C) showed no reaction in the plain and enzyme-treated panel at room temperature, 37°C and the AHG phase. The tube method being less sensitive could be the reason for negative reactions. The negative reaction with papain suggested antibodies to MNSs/Duffy system or HTLA antibodies such as anti-JMH, and anti-Ch/Rodger. However, weak pan-reactivity, which was destroyed by the enzyme, is more suspicious of HTLA antibodies such as anti-Ch, anti-Rg, or anti-JMH and unlikely to be anti-MNSs/Duffy.

Further tests of antibody titration proceeded which is a semiquantitative method used to determine the antibody concentration in a plasma sample and to compare the strength of antigen expression on different red cell samples. Serial dilution was done on the patient's plasma. Antibodies with HTLA characteristics generally have a titer >64, with most tubes showing consistently weak reactivity [2]. In this present case, the titration showed a weak reactivity with a titer of 128, suggesting HTLA antibodies. A plasma neutralization or inhibition test was performed by pooled plasma. The IAT using the neutralized plasma against papain-treated red cells showed the reactions were not neutralized/had no inhibition of antibody activity, excluding anti-Ch/Rodger (Fig. 1). Thus, an underlying HTLA, most likely anti-JMH was concluded. The test results of different immunohematological tests are summarized in Table 1.

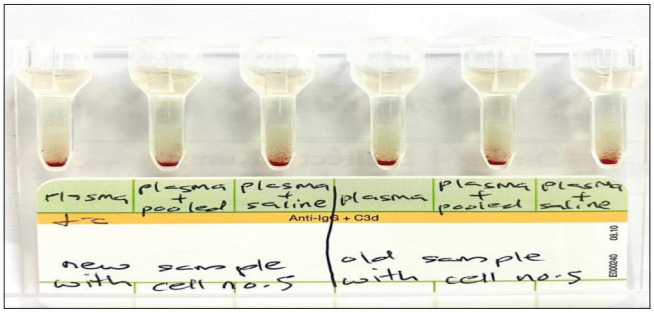

Figure 1: Plasma neutralization or inhibition test showed no inhibition of antibody activity by pooled plasma. Anti-Chido/Rodger is excluded by this

Table 1: Test results of different immunohematological test

Test done	Results
ABO and RhD Blood Group	O RhD positive
Rh genotype	CDe/CDe (R1R1)
DAT polyspecific	Positive (2+)
DAT monospecific anti-igG	Positive 2+
DAT monospecific anti-c3d	Negative
Antibody screening (CAT, 3 cell panel)	1+pan-agglutination
Antibody identification (CAT, 11 cell panel)	1+pan-agglutination
Antibody identification with papainized cell (CAT, 11 cell panel)	Negative
Antibody identification (tube method at RT, 37C and AHG phase, 11 cell panel)	Negative
AHG phase crossmatch	Compatible
Antibody titre	1:128
IAT with neutralized plasma	No inhibition of antibody activity

The cross-match was compatible with random group-O RhD-positive packed cells. Subsequently, the patient was transfused with 180 mL of group O RhD-positive, cross-matched compatible packed cells without any adverse events.

DISCUSSION

High-titer defines the reactivity of the antibody, which continues to be observed at high dilutions (>64 to as high as 2048). In contrast, low avidity is weak reactivity (1+ or less) with the corresponding antigen at the AHG phase due to weak bonds [2,3]. Several tools help to detect HTLA antibodies, such as titration studies, enzymes/chemicals treatment, and neutralization tests [2]. We have done all the tests mentioned in our case. The serological characteristics of HTLA include weak agglutination at AHG and are destroyed by enzymes, as seen in the pan-reactivity with 1+ reaction in our case. The titration study in our patient showed a high titer of 128 which agrees with the HTLA antibody. The neutralization test showed no inhibition, excluding the anti-Ch/Rodger and making anti-JMH the most likely antibody [4]. However, with our limited resources, we could not send for a confirmatory test to further prove our findings.

The pan-agglutination reaction poses a challenge in the immunohematological test, as in our case. The pan-reaction can

be due to autoantibodies, multiple alloantibodies, or antibodies to high-incidence antigens. In our case, autoantibody is excluded as the eluate was negative [6]. The suspected alloantibody was limited to the MNSs/Duffy system as the reactions were destroyed by enzymes, which were also excluded because these antibodies do not normally show pan-agglutination. Moreover, reactions of the same strength exclude multiple antibodies. Finally, anti-JMH was detected as the possible antibody causing pan-agglutination.

At present, there are six recognized high-prevalence antigens in the JMH system which are located on the Sema7A protein, GPI-linked glycoprotein CD108, encoded by the SEMA7A gene on chromosome 15 [4,7]. The JMH-1 antigen is usually known as JMH, while other JMH variant antigens are produced due to single nucleotide changes in the SEMA7A gene. There are reports of anti-JMH found primarily in older people [4,5]; however, in our case, it was present in a child. Anti-JMH is mainly IgG4, developed in acquired and transiently depressed JMH-negative people. Acquired antigen depression most commonly occurs in older people [8] and in individuals with underlying diseases such as paroxysmal nocturnal hemoglobinuria. In our case, the antibody probably has developed due to the underlying AML of the child. Although these antibodies may not be clinically significant, their presence may mask clinically significant antibodies and can cause a negative impact on the timely supply of blood and the safety of the blood transfusion. Resolution of such complicated cases is required to provide safe and effective transfusion.

CONCLUSION

This case report highlights a child with HTLA antibody, most likely anti-JMH, with drug-associated autoantibody in a limited resource setting with no means of molecular confirmation. Although anti-JMH is considered clinically insignificant antibodies, there are reports of transfusion reactions due to this antibody. Moreover, their presence causes a negative impact as they mask the clinically significant antibody and may cause a delay in the supply of blood. Therefore, it is crucial to exclude these antibodies and determine underlying clinically significant antibodies, to ensure a safe and effective transfusion. Good knowledge is essential for transfusion immunohematologists and clinicians to resolve such complicated cases.

REFERENCES

1. Kim TY, Hong YJ, Kim H, Park KU, Han KS. A case of anti-JMH antibody with high-titer, low-avidity characteristics: The first case in Korea. Korean J Blood Transfus 2017;28:155-62.
2. Bishop S, Trudell K. Detection and identification of antibodies. In: Harmening D, editor. Modern Blood Banking and Transfusion Practices. 7th ed., Ch. 10., United States: F.A. Davis; 2019. p. 232-55.
3. Das S, Priyamvada PS, Basavarajegowda A, Mathur A. Deciphering a delayed hemolytic transfusion reactions nightmare-case of Chido/Roger antibodies. Asian J Transfus Sci 2019;13:132-5.
4. Leger RM, Novotny AK. Uncommon blood groups. In: Harmening D, editor. Modern Blood Banking and Transfusion Practices. 7th ed., Ch. 9., United States: F.A. Davis; 2019. p. 212-31.
5. Hoppe B, Pastucha L, Seltsam A, Greinacher A, Salama A. Acute haemolytic transfusion reactions due to weak antibodies that *in vitro* did not seem to be clinically significant. Vox Sang 2002;82:207-10.
6. Kokoris SI, Kalantzis D, Moschandreou D, Papaioannou K, Grouzi E. Pan-agglutination on the indirect antiglobulin test. this is the challenge! Asian J Transfus Sci 2022;16:257-62.
7. Yuan Z, Wei Y, Chen X, He S, Cai K, Zhong M, *et al*. Anti-JMH alloantibody in inherited JMH-negative patients leads to immunogenic destruction of JMH-positive RBCs. Clin Exp Immunol 2021;205:182-97.
8. Gomes Vizzoni A, Medeiros da Silva FR, Barreto Bokel JP. Anti-Chido/Rodgers antibodies in a patient with infectious disease. Rev Cuba Hematol Inmunol Hemoter 2022;38:e1561.

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