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Case Report

한국의 3차 병원에서 동정된 항-LW 증례보고 3예

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Three Cases of Anti-LW Antibody Identification at a Tertiary Hospital in Korea

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The Landsteiner-Wiener (LW) antigen is a type of red blood cell antigen. Anti-LW appears in various situations, including alloantibodies, autoantibodies, and even transiently occurring antibodies. Anti-LW has similar characteristics to anti-D, so it can interfere with interpreting pre-transfusion tests and finding compatible blood. This paper introduces three cases in whom anti-LW was detected through antibody identification tests. All three cases were examined using the column agglutination technique with ID-DiaPanel (Bio-Rad, Hercules, CA, USA) on a LISS/Coombs card, ID-DiaPanel p (Bio-Rad) on a NaCl/Enzyme card, and ID-DiaPanel (Bio-Rad) on a LISS/Coombs card using red blood cells treated with dithiothreitol. The auto-control test, direct antiglobulin test, and umbilical cord blood test were also performed. In all three cases, the reaction with D-positive panel cells was stronger than that with the D-negative panel cells, and two of them showed a pan-agglutinated reaction in ID-DiaPanel p (Bio-Rad) with NaCl/Enzyme card. They were reported as anti-LW, and as in these cases, anti-LW can occur under a range of conditions and interfere with proper transfusion. Therefore, it is important to identify anti-LW accurately, and if anti-LW is present, the transfusion of D-negative ABO matched blood should be recommended because of the low expression of the LW-antigen. On the other hand, D-positive blood is not a contraindication when an urgent transfusion is needed. (**Korean J Blood Transfus 2022;33:39-45**)

Key words: Landsteiner-Wiener, Anti-LW, RBC antigen, Antibody identification

Introduction

The Landsteiner-Wiener (LW) antigen is one of the red cell antigens, which belongs to the 16th blood group system of the International Society of Blood Transfusion (ISBT). Landsteiner and Weiner [1] identified the LW antigen in 1940 and called it the "D-like" antigen because of its similar immunologic

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specificity to the D antigen. In 1963, Levine P. discovered the antigen had independent specificity from the D antigen and named the antigen "LW" after its discoverers [2].

Several cases of anti-LW appearing in variable situations have been reported. Anti-LW alloantibodies developed after sensitization by the non-self LW antigen during transfusion or pregnancy. Sometimes, the anti-LW autoantibody was detected in case of autoimmune hemolytic anemia [3]. Unusually, the anti-LW antibody occurred transiently with a loss of antigen in LW-positive person under variable conditions, including hematologic malignancy, infection, or pregnancy [4,5].

Anti-LW shows a similar pattern to the anti-D in antigen-antibody reaction, so the interpretation of pre-transfusion tests may be confused. Anti-LW reacts to D-positive red blood cells (RBC) more strongly than D-negative RBC because of the higher density of LW antigens in D-positive RBC [4,6]. Anti-LW is suspected when anti-D is identified in the patient, and the patient must have no history of drug administration and blood transfusion. Anti-LW showed a stronger reaction to the cord blood of infants than adult blood [7]. High titer anti-LW can agglutinate all random donor RBCs causing difficulties in finding compatible blood for transfusion. On dithiothreitol (DTT) or pronase-treated RBC, LW antigens are destroyed or reduced, and the reaction of anti-LW to these cells is then decreased or absent [3,8]. Patients identified with anti-D are diagnosed with anti-LW if the cord blood and DTT response are present; otherwise, they are diagnosed with anti-D.

Thus far, there have been few case reports and studies for anti-LW in Korea. This paper reports the identification of the anti-LW antibody in a tertiary hospital in Korea.

Case Reports

From July to September 2018, a request was made to examine unidentified antibodies of three patients from local medical centers. The samples were contained in ethylenediaminetetraacetic acid (EDTA) bottle and a plain tube.

An antibody-screening test (ID-Diacell I-II, Bio-Rad, Hercules, CA, USA) and antibody identification test were performed using ID-DiaPanel (Bio-Rad) with the LISS/Coombs card and ID-DiaPanel p (Bio-Rad) with the NaCl/Enzyme card that was treated with papain. The DTT-treated panel cells were tested using ID-DiaPanel (Bio-Rad) with the LISS/Coombs card. Auto-control test, direct antiglobulin test (DAT), and reaction to ABO-matched D-positive umbilical cord blood were also performed. Table 1 lists the test results.

1. Patient 1

An 88-year-old man diagnosed with a myocardial infarction tested positive in the antibody-screening test. He was typed as group B D-positive and did not have a transfusion history. The serum reacted with all D-positive panel cells in the identification test and did not react with D-negative panel cells except one cell, a trace in cell 4. The reaction intensities increased with papain-treated RBCs. The reactions with DTT-treated D-positive panel cells were negative, while a crossmatch with group B D-positive cord blood showed strong positive (4+). A crossmatch was performed with group B D-pos-

Table 1. Results of antibody identification tests of three patients

Panel cells	D	C	E	c	e	Patient 1			Patient 2			Patient 3		
						LISS/ Coombs	Enzyme	DTT	LISS/ Coombs	Enzyme	DTT	LISS/ Coombs	Enzyme	DTT
1	+	+	−	−	+	3+	4+	−	2+	dcp	−	1+	4+	−
2	+	+	−	−	+	3+	4+	−	2+	dcp	−	1+	4+	−
3	+	−	+	+	−	3+	4+	−	2+	dcp	−	trace	3+	−
4	−	+	−	+	+	trace	dcp	−	trace	dcp	−	−	4+	nt
5	−	−	+	+	+	−	−	nt	1+	dcp	−	−	3+	nt
6	−	−	−	+	+	−	−	nt	1+	dcp	−	−	4+	nt
7	−	−	−	+	+	−	−	nt	trace	dcp	−	−	4+	nt
8	+	−	−	+	+	3+	4+	−	2+	dcp	trace	1+	4+	−
9	−	−	−	+	+	−	−	nt	trace	dcp	−	−	3+	nt
10	−	−	−	+	+	−	−	nt	trace	dcp	−	−	4+	nt
11	−	−	−	+	+	−	−	nt	1+	dcp	−	−	3+	nt
Auto-Control						3+	−	3+	2+	dcp	nt	2+	3+	nt
DAT						3+			3+			3+		
Adult and Cord Blood*						3+/4+			1+/2+			1+/2+		

Abbreviations: dcp, double cell population; DAT, direct antiglobulin test; DTT, dithiothreitol; LISS, low ionic strength saline; nt, not tested.
*ABO types of blood were the same as each patient's, and Rh types were D-positive.

itive and D-negative adult blood, which resulted in positive (3+) and relatively weak positive (1+), respectively. DAT and auto-control tests were positive (3+). This patient was concluded as being "suggestive of Anti-LW", including the possibility of the anti-LW autoantibody.

2. Patient 2

A 76-year-old woman visited hospital due to septic shock. She had a history of pregnancy but no transfusion. She was typed as group B D-positive. The serology test was positive to the antibody-screening test and pan-agglutination, showing a strong reaction to D-positive cells in the antibody identification test. Double cell populations were observed in reaction with papain-treated panel RBCs, and the reactions were reduced with DTT-treated cells. DAT and auto-control tests were positive (2+/3+), and the reaction to cord blood (2+) was stronger than to adult blood (1+). The patient was concluded as "suspicious of anti-LW" considering the presence of another allo- or autoantibody.

3. Patient 3

An 82-year-old woman visited hospital because of chronic kidney disease, and pretransfusion tests were performed. She was group A D-positive and had a history of pregnancy, but no transfusion. Her serum was weakly positive to D-positive RBCs, and pan-agglutination to papain-treated RBCs was obser-

ved. The reaction intensity was higher with A D-positive cord blood (2+) than with adult blood (1+), and decreased with DTT-treated cells (−). DAT and auto-control tests were positive (2+/3+). We concluded as "suggestive of anti-LW".

Discussion

Since the "D-like" antigen was discovered in 1940, the nomenclature of the LW antigen was changed several times. There are four phenotypes of LW antigen according to the LW blood group system of ISBT: A reference alleles, *LW*05*, or *LW*A*, encodes LW:5 or LW (a+b−) and LW:6, or LW (a+b+); *LW*07* or *LW*B*, encodes an antithetical antigen LW:7, or LW (a−b+); *LW*05N.01* encodes the null phenotype, LW:6 or LW (a−b−). *LW*07* has a single nucleotide substitution, c.299A>G, and *LW*05N.01* has a deletion of 10 nucleotides, c.346_355del, from the *LW*05* reference allele. The variable population prevalence of LW (a+b−) is over the 90 percentiles [9], particularly the 99th percentile in the Korean population, and LW (a−b+) is rare [10].

The LW antigen is a glycoprotein, intracellular adhesion molecule (ICAM-4) encoded by the *ICAM4* gene on 19p13.2 [5]. The role of the LW antigen is not revealed definitely, but several studies suggest the LW antigen is expressed on RBCs and placenta, and involved in adhesion to endothelium, erythropoiesis island stabilization, and a vascular occlusion in sickle cell disease [11,12].

There are few reports on the occurrence of Anti-LW (Supplementary Table 1). Some showed that the anti-LW could be developed transiently in LW-positive people. In these transient cases, patients lose their LW antigen expression and produce anti-LW^{ab}, which causes incompatible results with the blood from all random donors. DAT is usually negative but can be positive because, at a later phase of transient anti-LW, the patient's antigens are expressed again, and anti-LW disappears gradually over several weeks or months. These transient anti-LWs can appear simultaneously with anti-D, in which the discrimination of antibodies becomes increasingly difficult. The conditions inducing transient anti-LW are variable, such as pregnancy, transfusion, Hodgkin's disease, bladder infection, and non-Hodgkin's lymphoma, but its pathophysiology was not discovered [4]. The patients reported were over 45 years of age, except one female who was 18-years old and pregnant. The nature of anti-LW could be transient or consistent. Additional tests, such as absorption and elution, monoclonal DAT, and LW genotyping, should be performed to elucidate the nature of anti-LW. In the present three cases, however, these tests could not be performed because of a shortage of blood samples.

The hemolytic potent of anti-LW is controversial. Celano et al. [13] reported the presence of anti-LW in acquired hemolytic anemia patients, and DeVeber et al. [14] suggested a possibility of fetal-maternal hemorrhage in a case where an LW antigen-negative mother was alloimmunized by fetal blood and developed anti-LW in her blood, while an LW antigen-positive infant showed a positive DAT result and jaundice two days after birth. Chaplin et al. [15] transfused incompatible D-negative RBCs, which were labeled with Cr^{51}, to a patient with anti-LW and revealed sustained RBC lifespan with no adverse reactions, which was in contrast to a report

by Herron et al. [16], where RBCs lifespan was reduced in mononuclear phagocyte assay and in vivo RBC survival study. Napier and Rowe [17] reported a case of developed anti-LW in a healthy male person after an anti-D immunization program, and showed that anti-LW did not cause hemolysis by in vitro experiments but reduced the lifespan of LW antigen-positive RBCs in vivo. Villalba et al. [18] suggested the clinical significance of anti-LW with monocyte monolayer assay. Davies et al. [19] reported a case of hemolytic disease of fetus and newborn, which was induced by the auto anti-LW of the mother that developed during pregnancy. The infant showed a positive DAT result and required phototherapy to solve the high bilirubin level. Shin et al. [6] reported a case in which a patient with anti-LW did not show a hemolytic transfusion reaction after transfusion with D-positive RBCs. Comprehensively clinical significance and hemolytic potent of anti-LW are uncertain because the cases are rare, and the results are heterogeneous. Instead of inducing intravascular hemolysis that damages multiple organs directly, anti-LW may promote extravascular hemolysis, resulting in a decrease in the RBC lifespan silently. More studies about LW antigen and anti-LW will be necessary to understand these points. If anti-LW is detected and compatible blood cannot be found, D-negative blood is primarily recommended because of the low expression of the LW-antigen, but D-positive blood is not a contraindication when an urgent transfusion is needed.

Overall, even in a region or population showing an extremely high prevalence of the single LW antigen phenotype, anti-LW can appear as a transient form without alloimmunization. A D-positive specific preference for Anti-LW makes it difficult to distinguish anti-LW from anti-D, and pan-agglutination characteristics may be interpreted as a non-specific autoantibody. Therefore, blood bank workers and specialists should be able to consider the possibility of anti-LW and identify precisely in suspicious situations. When anti-LW is revealed, pan-agglutinable potency of anti-LW may interfere with finding adequate blood donors for patients. In such a situation, D-negative ABO matched blood is recommended, but if there is no available D-negative blood, D-positive ABO matched blood must be given instead of delaying transfusion. There are scarce documents to evaluate the clinical significance of anti-LW. Hence, more studies and case discussions for anti-LW are necessary.

요 약

Landsteiner-Wiener (LW) 항원은 적혈구 항원의 한 종류이다. 항-LW는 다양한 상황에서 나타나는데 동종항체, 자가항체, 심지어 일시적으로 발생한 항체의 형태로도 나타난다. 또한 항-D와 유사한 성격을 가지고 있어 수혈 전 검사를 해석하는 것과 그에 따른 적합한 혈액을 찾는 데 방해가 될 수 있다. 본 저자들은 항체 동정 검사를 통해서 항-LW를 검출한 3개의 증례에 대해 보고하고자 한다. 3가지 증례는 모두 원주응집법을 이용해 Bio-Rad ID-DiaPanel 동정혈구와 LISS/Coombs card, Bio-Rad ID-DiaPanel-P 동정혈구와 NaCl/Enzyme card를 사용하여 검사하였고, DTT 처리를 한 동정혈구와 LISS/Coombs card를 사용한 검사가 시행되었다. 자가 대조 검사, 직접 항 글로불린 검사, 탯줄혈액 검사 또한 시행되었다. 세 증례 모두 D-양성패널세포와의 반응이 D-음성패널세포와의

반응보다 강했으며 이 중 2건은 enzyme card method에서 범응집현상을 보였다. 이들은 항-LW로 보고되었으며, 본 증례들에서 보듯이 항-LW는 다양한 조건에서 발생할 수 있으며 적절한 수혈을 방해할 수 있다. 따라서 항-LW를 정확하게 식별하는 것은 중요하며, 항-LW가 존재하는 경우 LW 항원 발현이 낮은 D-음성 ABO 매칭 혈액의 수혈을 1차적으로 권장하지만, D-양성 혈액 또한 긴급한 수혈이 필요할 때는 금기가 아니다.

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