Red Cell Antigens and Antibodies

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KEYWORDS

- Autoimmune hemolytic anemia • Autoantibody specificity
- Cold-reactive autoantibodies • Warm-reactive autoantibodies
- Direct antiglobulin test (DAT) • Genotyping

KEY POINTS

- Genotyping is helpful to support auto versus alloantibody specificity and is recommended whenever an apparent autoantibody demonstrates unexpected selectivity for a specific blood group system.
- Genotyping of patients with autoimmune hemolytic anemia (AIHA) is helpful in guiding transfusion therapy by avoiding alloimmunization and potentially reducing delays in treatment.
- Reactivity to Rh/Band 3 complex is more commonly seen in warm AIHA as demonstrated by the absence of reactivity with Rhnull cells.
- Reactivity to I antigen is more commonly seen in cold AIHA as demonstrated by the absence of reactivity with cord cells.
- Interference in routine compatibility testing can be addressed by demonstrating compatibility using adsorbed plasma or using units "antigen matched for clinically significant antigens" replacing "least incompatible" terminology. Clinics Care Points

INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is a heterogeneous condition that is characterized by shortened red blood cell (RBC) survival due to the presence of "warm-" or "cold-" reactive autoantibodies that bind to RBCs with or without complement activation. The severity of the anemia varies from mild to life-threatening. Multiple triggers can cause the production of antibodies that cross-react with self-RBC antigens, including disease, viral infection thought to be due to molecular mimicry between autoantigens and pathogens, or drugs; from breakdown in immune system tolerance

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to self-antigens; or from exposure to foreign antigens. Autoantibodies are also often seen in patients who are making alloantibodies, and common in patients who are chronically transfused and become alloimmunized. Identification of the specificity of the causative alloantibody in the plasma of the patient who also demonstrates autoantibody reactivity can be challenging. The target antigen is often not clear as autoantibodies are almost always panreactive (reactive with all test cells in laboratory testing) but can demonstrate relative specificity (weakly or non-reactive with cells lacking common antigens such I, or Rh), and target antigen expression can be depressed or masked on the patient's cells when autoantibody is present. Lastly, AIHA can be seen in specific clinical settings including pregnancy, transplantation, and treatment with cancer immunotherapy.

The direct antiglobulin test (DAT) is a key laboratory test that determines if RBCs were coated in vivo with immunoglobulin (Ig), complement or both, and is discussed in greater detail in this issue. Briefly, a positive DAT associated with anemia and hemolysis without other obvious cause is suggestive of AIHA but the final diagnosis is dependent on the clinical and laboratory findings and include hemoglobin and hematocrit values, reticulocyte count, bilirubin, haptoglobin, and LDH levels. The RBC autoantibodies may be of IgG or IgM isotypes, or less commonly of both IgG and IgM, or rarely of IgA isotypes, with or without the fixation of complement. Not all autoantibodies (or positive DAT results) detected are associated with hemolysis or anemia.

The DAT results and the temperature at which the autoantibodies bind optimally to RBCs assist with the determination of the type of AIHA. Warm autoimmune hemolytic anemia (WAIHA) is the most common type, accounting for 60% to 75% of cases, and autoantibodies generally react at temperatures $\geq 37^{\circ}C$. Other types of AIHA include cold agglutinin disease (optimal reactivity less than 37°C), mixed-type AIHA (typified by cold agglutinins that react at or above 30°C), paroxysmal cold hemoglobinuria (PCH), and drug-induced hemolytic anemia. More information on the diagnosis and differentiation of AIHA can be found in this issue by Go and colleagues

APPARENT RED CELL BLOOD GROUP ANTIGEN SPECIFICITIES

In the vast majority of cases, patient plasma will react with all RBC samples tested, and a relative or apparent specificity is not found, or may not be able to be determined by the hospital laboratory without testing uncommon or rare cells lacking high prevalence antigens. This requires referring the sample to a regional reference laboratory, which may be helpful to guide the selection of blood in some situations if transfusion is required and the reactivity appears to have a possible blood group specificity.

Relative specificities, which are seen when testing the plasma, differ according to the type of AIHA. The most common specificity encountered among warm-reactive autoantibodies is to the Rh complex, as reflected by the observation that the antibodies react with all cells commonly tested, but do not react, or react only weakly, with Rh_{null} (lack all Rh antigens) or D– – (lack RhCE antigens) cells. Rarely, some have apparent "mimicking" specificity for a single Rh antigen such as Rhe or RhD or RhC.[1] These autoantibodies are referred to as mimicking because they can be adsorbed (removed) from the plasma by red cells lacking the antigen. If associated with recent transfusion, these "autoantibodies" can represent the immune response in an individual with altered RH alleles, with the antibody cross-reactive with the patient's own red cells. Genotyping is helpful to support auto versus alloantibody

specificity and is recommended whenever an apparent autoantibody demonstrates selectivity for a specific blood group system.

Specificities to antigens in other blood group systems have occasionally been reported (**Table 1**). The autologous nature of an antibody may not always be obvious if the target antigen expression is masked, or transiently suppressed when autoantibody is present. Some RBCs can escape antibody-mediated hemolysis through selective loss of the antigen being recognized by autoantibodies (or even alloantibodies). This interesting phenomenon has been observed with antigens in several blood group systems. Antigen suppression has most often been observed with Kell blood group antigens, especially Kp^b.[2] Vengelen-Tyler et al.[3] reported a patient with a long history of idiopathic thrombocytopenic purpura who developed a potent antibody against a high-prevalence Kell antigen. His RBCs had profound depression of Kell antigens, but not of antigens of other blood groups. Transfusion of incompatible blood was well tolerated perhaps because the transfused red cells also showed acquired loss of Kell antigens. When the Kell-related antibody disappeared, Kell antigens reappeared on his RBCs and serum stored from the initial investigation now reacted with his freshly collected RBCs. Antigen loss or reduced expression has also been reported with Rh, Kidd, Duffy, Lutheran, LW, Colton, Gerbich, En^a, AnWj, and Sc1 antigens,[1] but it is important to rule out that the antigen is not detected (masked) due to interference from Ig coating the cells. If antigen suppression occurs, the patient's RBCs may test negative in the DAT although circulating autoantibody is present.

AIHA, after viral infection or vaccination occurs much more often in children than in adults. The most common autoantibody specificity is to I or IH. Very rarely, the autoantibody associated with infection may demonstrate blood group specificity. Giovannetti and colleagues[4] reported the case of a 5-year-old child with severe WAIHA due to complement-binding autoanti-Jka that was associated with Parvovirus B19 infection.

Table 1
RBC antigenic specificities reported in AIHA, characteristics of the DAT and autoantibody

AIHA Category	Autoantibody Specificity	DAT	Autoantibody
Warm autoimmune hemolytic anemia (WAIHA)	Rh complex, single Rh antigens (eg, e, E, C, Ce, c, D) Band 3 Also: Wr^b, En^a, S, LW, U, Ge, Sc1, K, Kp^b, Ku, Jk^a, Jk^b, Fy^a, AnWj, P^k, Vel	IgG or IgG + C3 or C3	IgG - binds optimally at 37°C; ~35% bind RBCs at 20°C
Cold agglutinin disease (CAD)	I/i Also: Pr, M, P	C3	IgM - binds optimally below 37°C
Paroxysmal cold hemoglobinuria (PCH) Donath–Landsteiner test positive	P Rarely: I, i, Pr, p	C3 Rarely IgG detected by special methods	IgG complement-binding biphasic hemolysin Binds to RBCs at low temperatures; hemolysis occurs at ~37°C
Mixed AIHA	IgM against I/i IgG panreactive	IgG + C3 or C3	IgG reactive by IAT at 37°C IgM agglutinating at ~30°C

Abbreviations: AIHA, autoimmune hemolytic anemia; DAT, direct antiglobulin test; IAT, indirect antiglobulin test.

SPECIFICITIES ASSOCIATED WITH COLD-REACTIVE AUTOANTIBODIES

Cold Agglutinin Disease

Cold agglutinin disease (CAD) accounts for 10% to 15% of AIHA cases. It is associated with autoantibodies that can directly agglutinate saline suspended RBCs at low temperatures (maximally at 0°C to 5°C); the agglutination can be reversed with warming. The DAT result is positive with anti-complement only as RBC-bound antibodies dissociate from RBCs at 37°C. Blood samples from patients with CAD, if not collected and maintained at 37°C until the plasma/serum is separated from the RBCs, often demonstrate spontaneous agglutination (the cold-reactive autoantibody agglutinates the autologous RBCs in vitro). This can cause problems with ABO/RhD determination and typing for other antigens.

The specificity of most cold-reactive autoagglutinins is anti-I; less commonly the specificity is anti-i. The I antigen is strongly expressed on all RBCs from adults (except on RBCs of the rare adult i phenotype) but not on RBCs from cord samples, whereas the reverse applies to i antigen. Autoanti-I is found in the plasma of most healthy people but rarely have a titer above 64 at 4°C. In contrast, the potent autoanti-I (titers are 1000 or higher) implicated in CAD and found in patients with lymphomas or chronic lymphocytic leukemia are mostly monoclonal (IgM, rarely IgG), with a broader thermal amplitude reacting at temperatures up to 30°C. Transient polyclonal or oligoclonal anti-I may result from infection, in particular by *Mycoplasma pneumoniae*. Anti-i, found much less often, is most associated with infectious mononucleosis and with immunodeficiency. Autoanti-i may be IgM, IgM plus IgG or IgG only. Rarely, specificities detecting epitopes on glycophorin A (GPA) such as anti-Pr or anti-M are seen in CAD, and further described in the section later in discussion.

Paroxysmal Cold Hemoglobinuria

Paroxysmal cold hemoglobinuria (PCH) is a rare form of AIHA and occurs secondary to a viral infection, especially in young children. With the increasing rise in the number of cases of syphilis in recent years (see Centers for Disease Control and Prevention) it should be remembered that historically PCH was associated with this disease.

PCH is caused by a cold-reactive complement-binding IgG antibody with specificity for the P antigen, an antigen expressed on the RBCs of all people except those with the rare p phenotype. The antibody, often referred to as a biphasic hemolysin, binds to RBCs at low temperatures but hemolysis does not occur until the complement-coated RBCs are warmed to 37°C. The antibody rarely reacts above 4°C and does not impede pretransfusion testing. In most cases, transfusion is not required but when it is, patients respond well to “random” RBC units; rarely have p phenotype RBCs been required. P antigen is expressed on many other cell types and tissues, including skin fibroblasts. The occurrence of cold urticaria in PCH may be related to the presence of P on skin fibroblasts. The standard diagnostic test for PCH is the Donath–Landsteiner test.[5]

Antibodies to Glycophorin Molecules

The most abundant cold autoantibody specificities after anti-I and anti-i are anti-Pr. These antibodies detect the protease-sensitive determinants on O-linked sialoglycoproteins that are predominantly found on GPA and GPB. Anti-Pr are IgM antibodies and are difficult to distinguish from (auto) anti-En^a or (auto) anti-Wr^b specificities but the distinction is mostly only of academic value as blood that lacks these antigens is almost impossible to acquire. Wr^b antigen is located on band 3, the molecule that

carries the Diego antigens, and not on GPA. However, Wr^b expression is dependent on the interaction between GPA and Diego in the RBC membrane and Wr^b expression can be altered or suppressed by changes in GPA. Autoantibodies to band 3 and in particular to Wr^b are a common finding in AIHA.[6] This group of autoantibodies has all been shown to activate complement and been associated with acute intravascular hemolysis and fatal or life-threatening AIHA.[7] For some patients, the clinical effects were far more severe than would be predicted from the serologic characteristics of the antibodies. A novel antibody-mediated mechanism proposed by Brain and colleagues[8] suggests the hemolysis may be independent of the action of complement and macrophages. He proposes that antibodies to GPA may induce lipid bilayer exposure and cation permeability; in particular, the binding of the antibodies to cell surface sialoglycoproteins may increase membrane phosphatidylethanolamine exposure and induce a Ca^{2+} leak.

TRANSFUSION CONSIDERATIONS IN AUTOIMMUNE HEMOLYTIC ANEMIA

Most patients with AIHA will require transfusion support with red cell products. The presence of warm- or cold-reactive autoantibodies can complicate pretransfusion testing and the safe selection of blood. As autoantibodies are directed against highly prevalent antigens, routine cross-matching is often unable to identify compatible RBC units. In the presence of autoantibodies, the failure to identify an underlying alloantibody may lead to a (hemolytic) transfusion reaction. Therefore, the aim of pretransfusion testing for patients with AIHA, just as it is for all patients who require transfusion, is to identify (clinically significant) underlying alloantibodies.

The extent of the interference will depend on the level of free antibody in the plasma, the phase of reactivity, and the potency of the autoantibody but also may cause problems with typing for ABO/Rh and other antigens. Studies of patients with warm autoantibodies have reported that the concurrent presence of alloantibodies ranged from 10% to 53% (reviewed by Zinman and colleagues[9]) or 12% to 40% (reviewed by Delaney and colleagues[10]). Underlying alloantibodies are a major hazard of transfusion for these patients, and methods to mitigate the interference of autoantibodies is labor-intensive and time-consuming as detailed in this issue by Jacob and colleagues The standard of practice for most transfusion laboratories is to perform either an auto or alloadsorption (or send to a reference laboratory) to remove the autoantibody and test for underlying alloantibodies at initial diagnosis. Transfusion of donor units antigen matched for more than ABO is an option that may eliminate the need for repeat patient workups if additional transfusion is required. This avoids the use of "least incompatible" units[11] and can be replaced with "compatible for extended blood group antigens." Transfusion of RBCs that are selected based on the patient's extended phenotype (eg, D, C, E, e, K, Jk^a, Jk^b, Fy^a, Fy^b, S, and s) can provide a significant measure of safety as they avoid the patient being immunized to antigens absent from their RBCs. The availability of extended antigen typing by DNA-based assay makes this a feasible option[12] (see later in discussion). The adoption of such an approach requires informed discussion between transfusion medicine staff and clinicians caring for patients with AIHA.

If an autoantibody has a clear-cut blood group specificity and the patient is actively hemolyzing, it is desirable to provide blood lacking the antigen as antigen-negative RBCs may survive longer than the autologous RBCs and may avoid an incompatible cross-match. In some cases that approach may come with the potential risk of exposing the patient to an antigen that they do not express, for example,

providing blood negative for e antigen (which will be E+) when the patient lacks E antigen.

Generally, pretransfusion testing in the presence of cold autoantibodies is less labor-intensive as the antibody often does not react at 37°C and can be circumvented by performing testing at 37°C.

EXTENDED ANTIGEN TYPING BY DNA METHODS

No matter the approach used to remove the autoantibody to detect underlying alloantibodies, be it autoadsorption on the patient's own cells or alloadsorption (differential adsorption), discussed in detail in this issue, obtaining an extended antigen profile on the patient by DNA based typing is recommended.[12] A strongly positive DAT due to Ig coating the cells can interfere in antigen typing, most often associated with false-positive typing and/or spontaneous agglutination, but false-negative results due to antigen blocking can also occur. Removal of immunoglobin bound to the patient cells involves chemical treatment that is time-intensive and can weaken the expression of some antigens. A DNA-based approach offers more information at lower cost by testing for all common antigens in a single assay. The DNA blood group antigen profile also offers the opportunity to use this information to guide transfusion therapy with the potential to avoid exposure to antigens known to be highly immunogenic (K, RhC, RhE), or to transfuse the patient with red cells lacking common antigens that the patient also lacks, referred to as prophylactic antigen matching (PAM). Just as importantly, the extended antigen profile reveals what alloantibodies the patient may be at risk to make. This information can decrease the complexity of the laboratory workup, can reduce the number of repeat workups, and potentially avoid delay for subsequent transfusions and reduce costs.[12,13]

AUTOIMMUNE HEMOLYTIC ANEMIA ASSOCIATED WITH TRANSPLANTATION AND ANTICANCER DRUG THERAPY

There are an increasing number of reports of AIHA associated with transplantation and following treatment with anticancer drugs. AIHA can be particularly severe and life-threatening after allogeneic hematopoietic stem cell transplantation (HSCT)[14] and treatment with anticancer checkpoint inhibitors (CPIs), as described in this issue.[15]

Passenger lymphocyte syndrome (PLS) results when the donor lymphocytes passively transferred within the graft produce antibodies against the recipient RBCs. This generally can occur 3 to 24 days posttransplant and is usually mild and transient and primarily involves group O donors and ABO antibodies. However, antibodies to blood group antigens other than A and B associated with passenger lymphocytes have caused hemolytic anemia, including anti-Jk^a following allogenic peripheral blood progenitor cell (PBPC) transplantation.[16] PLS has also been seen in patients transfused with allogeneic natural killer cells for the treatment of solid malignancies.[17]

AIHA after allogeneic HSCT has an incidence between 4% and 6%[14] and both warm and cold autoantibodies can be observed. Severe immune hemolysis is associated with high mortality and is challenging to treat due to concomitant factors including infection, graft failure, CMV reactivation, and GVHD. The DAT is almost always positive and may be positive for specific alloantibodies characteristic of delayed hemolytic transfusion reactions, or for donor-derived antibodies produced by passenger lymphocytes, and often accompanied by panreactive autoantibodies. AIHA in allo-HSCT is often reticent to standard therapies, although rituximab and

several new options, including daratumumab, sirolimus, bortezomib, abatacept, and complement inhibitors are increasingly being used for this very serious complication.[18,19]

Antitumor immunotherapy, specifically CPIs that reactivate T lymphocytes to recognize cancer cells by blocking CTLA-4 or PD-1 are effective in numerous types of cancer. Potentially fatal AIHA has been reported.[15] Most cases were IgG positive warm AIHA; CADs were rarer. All were severe, with 80% of cases developing transfusion-dependent anemia, and the risk seemed higher with PD-1 or PD-L1. Mortality was as high as 17%.[15,20]

TRANSFUSION CONSIDERATIONS FOR AUTOIMMUNE HEMOLYTIC ANEMIA ASSOCIATED WITH PASSENGER LYMPHOCYTE SYNDROME, ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANTATION, AND CHECKPOINT INHIBITORS

As in primary AIHA, the presence of autoantibodies directed against highly prevalent antigens interfere with routine cross-matching methods, and like primary AIHA, the challenge and concerns are to identify any underlying alloantibody specificities to transfuse RBCs lacking the antigen(s). Incompatibility associated with PLS and solid organ transplant is often transient and usually involves ABO antibodies, which can be addressed by transfusion with Group O donor units, or antigen-negative RBCs when the antibody is directed to other than A or B antigens.

However, with allo-HSCT, there is heightened concern and risk of underlying patient immune response to engrafting foreign donor red cell antigens, as well as risk that donor passenger lymphocytes are responding to recipient RBCs antigens. Transfusion management of post–allo-HSCT is complex and extended phenotyping is advisable to guide therapy to provide the best matched RBC units, as transfusion may lead to (additional) alloantibody production causing serious acute or delayed hemolytic transfusion reactions. A close collaboration between clinicians and the transfusion service is advisable for the best management of transfusion support in post–allo-HSCT.[21] Consideration for the best choice of red cells for transfusion therapy can be aided by the consideration of the pretransplant RBC extended phenotype of the patient and the extended phenotype of the transplant donor. If recipient pretransplant sample is not available, extended typing using buccal swab DNA should be performed.[12]

SUMMARY

AIHA is the result of the increased destruction of RBCs in the presence of anti-RBC autoantibodies and/or complement. Autoantibodies may be of undefined specificity, reacting with all RBCs tested or may have an apparent specificity. Those with a definable specificity have targeted RBC antigens in many blood group systems but Rh, Kell, I, and i predominate. Suppression of the target antigen concurrent with autoantibody formation may make it impossible to distinguish allo-from autoantibody by serologic tests (eg, anti-Kp^b, anti-e) and antigenic variation should be ruled out by genotyping. Increasingly, AIHA is being reported in patients following allogeneic HSCT and treatment with anticancer CPIs. Autoantibodies, whatever their etiology, interfere with the pretransfusion testing of patients requiring RBCs transfusion making compatibility testing complex and labor-intensive. Transfusion of RBCs that are selected based on the patient's extended phenotype (eg, D, C, E, e, K, Jk^a, Jk^b, Fy^a, Fy^b, S, and s) can provide a significant measure of safety as they avoid the patient being immunized to antigens absent from their RBCs. The availability of extended antigen typing by DNA-based assay has made this a feasible option.

CLINICS CARE POINT

- Pretransfusion and compatibility testing for patients with autoimmune hemolytic anemia (AIHA) is complicated and prolonged by the presence of warm-reactive autoantibodies that may mask underlying alloantibodies.
- Performing an extended blood group antigen profile and choosing donor units based on avoiding the stimulation of blood group alloantibodies can increase transfusion safety for patients with AIHA.
- If the plasma of a patient with AIHA demonstrates an antibody to a high prevalence antigen it is essential to determine if it is allo or autoantibody to avoid delay in finding blood for transfusion and to use rare resources appropriately.
- A positive result in the DAT is not an indication that the patient is actively hemolyzing.
- The Donath–Landsteiner test is diagnostic of paroxysmal cold hemoglobinuria (PCH)

CONFLICT OF INTEREST

The authors declare no competing interests.

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