RiSE

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For Continuing Education Use

Lot No. 03806 **Expiration Date: March 27, 2015**

EXPECTED RESULTS:

1C (Patient EG)	1S (Patient EG)	2C (Donor DV)	3C (Donor FG)
ABO: O **Rh:** D+ C- E+ c+ e- **Other Typings:** C^W-	**ABO:** O **Unexpected antibodies:** Anti-C^W	**ABO:** O **Rh:** D+ C+ E- c- e+ **Other Typings:** C^W-; Compatible with EG's serum	**ABO:** O **Rh:** D+ C+ E- c- e+ **Other Typings:** C^W+; Incompatible with EG's serum

DISCUSSION:

The reactivity of EG's serum with the red cells of donor FG might easily have been missed. An antibody detection test (antibody screen) may well have been nonreactive – depending on the method used. In that event, a computer-crossmatch may have been employed or serological testing limited to an immediate spin test. EG's history may have suggested there was more to the story – the possibility of a prior antibody – although it might still have been assumed that a negative antibody screen ruled out the presence of an antibody. Fortunately, the instructions for RiSE include crossmatching the donor red cells with the patient's serum; revealing the incompatibility, unless only an immediate spin crossmatch was performed. Once this reactivity was detected, the next logical step would have been to test EG's serum against a panel of red cells for antibody identification. Such panels from commercial sources nearly always include a C^W+ sample. Reactivity with these cells would suggest anti-C^W, although tests with additional C^W+ samples would be required to confirm the specificity. Such cells would most easily be obtained from different commercial cell panels.

Anti-C^W is actually a somewhat common alloantibody, although many examples are in sera that also contain other antibodies. Bowman and Pollack found anti-C^W at a rate of 1 per 1,100 samples tested.[1] Anti-C^W has caused hemolytic disease of the fetus and newborn (HDFN).[2] This may be mild, though moderate to serious HDFN occasionally occurs.[3-6] It is quite possible that EG developed her anti-C^W through pregnancy. Her history suggests the antibody may have been detected during her third pregnancy quite some years ago, although it may not have caused significant HDFN. EG's husband, the presumed father of her children and source of any C^W antigen on the children's red cells, is now deceased and unavailable for testing; but it is suggestive that his cousin, donor FG, is C^W+, demonstrating the presence of C^W within the family.

Having identified anti-C^W in EG's serum, it would have been wise to confirm that donor FG's red cells really were C^W+. Many sera that contain antibodies to one low-prevalence antigen frequently contain antibodies to other low-prevalence antigens. Anti-C^W is often one component of such sera. Thus FG's red cells might have been incompatible for some other reason. They may have carried a different low-prevalence antigen to which EG also had antibody, perhaps one missing from most commercial antibody identification panels.

Its presence within the family is significant, for C^W is a relatively low-prevalence antigen, part of the RH blood group system. In most populations, only about 2% or fewer are C^W+. There is a higher prevalence in some European populations, notably among Latvians (about 9%) and Finns (about 4%).[7-9] This is why, though, *where* antibody detection tests were performed becomes important. Because of its prevalence rate within European populations, antibody detection cells used in Europe typically include C^W+ red cells. In North America, (and elsewhere), C^W+ cells are rarely selected for use as screening cells. Thus, most anti-C^W are discovered

when a full panel is tested (usually as a result of the suspected presence of an antibody *other* than anti-C^W) or when a C^W+ donor is encountered by chance.

Just as it may cause HDFN, anti-C^W can also cause transfusion reactions. If the presence of the antibody is known, transfusion reactions are easily avoided since C^W- donor units are readily available. As with other antibodies to low-prevalence antigens, transfusion reactions may potentially occur when the antibody screen is negative and an antigen-positive donor unit is selected, then transfused without a serological crossmatch (or "full" serological crossmatch, including indirect antiglobulin test) which may not be sufficient to detect the antibody.

Like most Rh antibodies, anti-C^W typically react at indirect antiglobulin tests (IAT), but may agglutinate C^W+ red cells in other phases of testing. In our tests, EG's antibody reacted weakly at 37C and moderately at IAT using traditional tube. Using Immucor's Capture-R® solid phase system, its reactivity was very strong. *[Reaction strengths in your laboratory may have varied, depending on multiple factors such as the antigen expression on the particular red cells tested, incubation times and methods used.]*. Enhancement media, such as polyethylene glycol (PEG), typically enhance reactivity of anti-C^W, as do tests using enzyme-treated red cells. Although most anti-C^W are stimulated by transfusion or pregnancy, some examples occur "naturally" – without prior exposure to C^W+ red cells.[5] These may be IgM antibodies, but can also include IgG forms.

Our understanding and interpretation of anti-C^W and the C^W antigen has changed over the years.[10,11] At first, *C^W* seemed to be an allele to *C* and *c*. Most anti-C react (to some extent) with C^W+ cells, so it was believed that all C^W+ cells carried some C antigen. Most examples of anti-C were thought to be "anti-CC^W", with an inseparable anti-C^W component. Much effort was spent attempting to explain this serological relationship. Eventually, red cells were discovered that carried the C^W antigen but not the C antigen.[9] Ultimately it became apparent that C^W is more simply a low-prevalence antigen carried on the RHCE protein, and that most, though certainly not all, C^W+ cells are also C+.

Anti-C^W was first described in England by Callender, Race and Paykoç in 1945. A more detailed report followed the next year.[12,13] The serum in which it was first found was quite interesting, for it also contained anti-c, anti-N, the first example of anti-Lu^a, and another antibody called anti-Levay. Three decades later, Levay was shown to be an antigen in the Kell blood group system and was re-named Kp^c.[14]

The "W" in the term "C^W" comes from "Willis", the name of the first person whose red cells were found to be positive for the antigen. The "W" should, therefore, be capitalized. C^W is also known as RH8.[7]

C^W is believed to be allelic to two other Rh genes: *C^X* and *MAR*.[15] MAR (RH51) is a high-prevalence factor, and both C^W or C^X are its antithetical low-prevalence antigens. The antigens occur in the first extracellular loop of the RHCE protein. The presence of the C^W antigen is associated with a point mutation in *RHCE*, leading to an amino acid substitution in the RHCE polypeptide – arginine (Arg) replacing glutamine (Gln) at position 41. A different substitution, at position 36, creates C^X (RH9).[16] The expression of C may be altered and weak on C^W+ and C^X+ red cells. Like C^W, the C^X antigen is also more common among Finns, where it has a similar prevalence of about 4%.[7]

Issitt and Anstee have pointed out that immune anti-C^W resulting from transfusion most often occur in patients with anti-c.[2] This is probably because patients with anti-c are given c- red cells, which are thus C+. Since most C^W+ red cells are C+, the chances are greater that selected C+ c- cells will be C^W+.

Additional Low-Prevalence Antigens within the Rh Blood Group System

The Rh system contains low-prevalence antigens besides C^W and C^X. Virtually all are less common than C^W in the general population, with most found in less than 0.01% of random individuals. Most are associated with variant Rh genes, especially D variants, and many also show aberrant expression of common C/c or E/e antigens.[2,7]

V (RH10) occurs in about 1% of Caucasians, but is much more common (about 30%) among U.S. African Americans. Most V+ red cells are also positive for the antigen **VS (RH20)**, which is in turn related to another low-prevalence antigen, **hr^H (RH28)**. VS is often associated with weakened C and/or e antigens. Although low-prevalence over-all, in African American populations 25-40% may be VS+.

E^W (RH11) is rare but a bit more prevalent among people of German ancestry. Here the "W" stands for weak. Most, though not all, anti-E react with E^W.

Go^a (RH30, Gonzales) is associated with the partial D antigen produced by category DIVa individuals. Anti-Go^a may occur alone, but often also appears with anti-Rh32, detecting yet another low-prevalence Rh antigen. When anti-Go^a and anti-Rh32 occur together, the two specificities are not separable by typical methods such as adsorption. **Rh32** is associated with the partial D category DBT. Anti-Evans (-Rh37) also may occur alone but when associated with anti-Go^a or anti-Rh32, it cannot be isolated. **RH37** is found on D•• red cells, with a high level of D but no C, c, E or e.

Be^a (RH36, Berrens), although rare, is most often found in people of Polish or German ancestry. Be(a+) red cells usually have weak c, e and f antigens. Anti-Be^a is an immune antibody that has caused HDFN.

Tar (RH40, Targett) is associated with the partial D category DVII, but is also found on certain other D-variant red cells.

JAL (RH48) is produced by different Rh gene complexes. When found in Caucasians, it has been associated with weak C antigens; in African Americans, with a weak c antigen. In either instance, the e antigen may also be weak.

STEM (RH49) is associated with an altered e antigen. About 65% of hr^S– and 30% of hr^B– donors in South Africa were found to be STEM+. The genetic basis has recently been established.[17] Anti-STEM is quite rare.

FPTT (RH50) got its name when it was found among workers at the French Post Telegraph and Telecommunications. It, too, is associated with certain partial D phenotypes.

BARC (RH52) was associated with the partial D category DVI. Its name is derived from the Badger American Red Cross, the laboratory that first found the antibody.

JAHK (RH53) is found on rare cells of the r^G phenotype. It has not been associated with r''^G cells.[1]

CENR (RH56) is associated with a hybrid gene in which specific exons from an *RHCE* gene replace those in an *RHD* gene. It was found in a C^W+ individual, with weakened C and e antigens.[19]

Commercial Anti-C^W reagents may not always be available. It can be useful to save specimens such as EG's serum when they contain potent examples of antibody. Such samples serve as a good "second source" reagent, even when commercial Anti-C^W is available, and they can be especially important when it is not. They can provide a useful screening antiserum to identify prospective C^W– cells. The typings can perhaps then be confirmed with a commercial reagent. Another approach in some situations is the use of PCR-based DNA analysis; such testing can also be useful in predicting possible cases of HDFN and in circumventing some of the serological complexities due to C/C^W associations.[20]

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