A readily available assay for anti-immunoglobulin A: is this what we have been waiting for?

Although anaphylactic transfusion reactions due to underlying immunoglobulin A deficiency (IgAD) are rare, it is not uncommon for transfusion medicine physicians to encounter patients with transfusion reactions with respiratory distress or hypotension, where the specter of anaphylaxis is raised. In such cases, IgAD with associated anti-IgA as the underlying cause must be excluded. Another common scenario is a patient with a purported history of IgAD, requiring a judgment in a limited time window as to whether special IgA-deficient blood components are needed for transfusion. In the majority of such cases, IgAD is not present in the patient, nor has it been an etiologic factor in a previous transfusion reaction. However, in most urgent situations, there are no diagnostic tests readily available to help us exclude the presence of IgAD or anti-IgA.

Anaphylactic transfusion reactions are acute and potentially life-threatening events, and therefore it is incumbent upon physicians to identify at risk individuals and provide them with appropriate blood components to prevent such reactions. Severe anaphylactic reactions associated with IgAD and mediated by anti-IgA have been reported since 1968.1 There have been more than 40 case reports in the literature, but the true incidence of IgA anaphylactic transfusion reactions is still unknown. As recently pointed out by Sandler,2 many of the older reports of IgA anaphylactic transfusion reactions may actually represent examples of other entities, such as unrecognized transfusion-related acute lung injury, which may only have relatively mild respiratory distress.3 Other cases may be secondary to a variety of blood-soluble factors, such as latex, antibiotics, activated platelet (PLT) membrane fragments or PLT-derived microparticles, or cytokines generated in stored blood components.4,5

In Japan, where IgAD is rare, anti-haptoglobin antibodies are responsible for more anaphylactic transfusion reactions than anti-IgA.6 Furthermore, of the 359 samples referred to the American Red Cross National Reference Laboratory for suspected IgA anaphylactic transfusion reactions between 1978 and 1998, anti-IgA was identified only in 18% of the cases,7 suggesting that IgAD is only one of many causes for anaphylactic transfusion reactions. If anti-IgA can be shown to be absent in such cases, then IgA anaphylactic reactions can be essentially excluded, rendering provision of IgA-deficient blood components for future transfusions unnecessary.

In many ethnic populations, IgAD is the most common primary immune deficiency. Among Caucasian persons, IgAD is often quoted to have a prevalence of 1 of 500 to 700 individuals. Although most patients are asymptomatic at the time of diagnosis, up to 80 percent show a predilection for sinopulmonary and gastrointestinal infections, as well as autoimmune disorders when followed for up to 20 years.8 IgAD is rarely of immediate clinical concern, except in the setting of blood transfusion, and only patients with severe IgAD whose plasma contain anti-IgA are at risk for IgA-mediated anaphylaxis. Such reactions in these individuals can be prevented by providing IgA-deficient blood components. Red blood cells (RBCs) from normal donors can be rendered IgA-deficient with thorough washing to minimize the plasma content, but plasma products must be prepared from IgA-deficient donors. PLTs can be washed, but the procedures required to remove enough plasma to prevent reactions can damage PLTs, limiting their recovery and survival.

Registries of IgA-deficient donors have been established in the United States, Canada, Europe, and Asia.9 To ensure that IgA-deficient products contain only negligible amounts of IgA, most collection centers use stringent criteria to qualify potential donors as IgA-deficient. For example, all donors in the American Rare Donor Program (ARDP) database must have IgA levels less than 0.05 mg per dL, measured twice with high-sensitivity IgA assays. In most populations, only about half of the individuals who meet the clinical criteria of IgAD (serum IgA < 7 mg/dL) would have IgA concentration low enough to be qualified as an IgA-deficient donor.10 The Canadian Blood Services, in addition to using the same criterion of IgA level, also excludes donors with detectable anti-IgA. As a result, only 34 eligible donors were identified after screening 38,759 donor samples in one study.11 Therefore, IgA-deficient components are a scarce and precious resource that should be allocated with care and reserved for patients at risk for anaphylaxis.

On the other hand, the need for such rare products for patients with a reported history of IgAD or anaphylactic transfusion reaction cannot be convincingly established in many cases. The current prevailing clinical definition of IgAD (serum IgA level below 7 mg/dL in an individual older than 4 years of age) was chosen in part because IgA concentrations cannot be measured reliably below this...
cutoff with nephelometry, the most widely available method for measuring IgA levels. Severe IgAD has been defined variously as an IgA level below 0.05 to 0.5 mg per dL, and a higher-sensitivity assay for measuring IgA, such as passive hemagglutination inhibition,12 solid-phase RBC adherence assay,13 or enzyme-linked immunosorbent assay14 is required to establish the diagnosis. Distinction between mild and extreme deficiency is important, because true anaphylactic reactions probably occur only in patients with severe deficiency, who make anti-IgA of broad (class-specific) rather than limited (subclass-specific) specificities.8,15,16

In our experience, many patients who are said to be IgA-deficient do not have documented IgA levels available, and many have only partial or age-related, transient forms of IgAD upon further investigation and do not require provision of IgA deficient blood products.

Therefore, when time permits, the necessity for such rare products should be confirmed. Such investigation should consist at minimum of a measurement of IgA level by the most expedient method. If some degree of deficiency is established, patients at higher risk for anaphylactic transfusion reactions can be further identified by demonstrating the presence anti-IgA.2,10

However, the above approach is rarely feasible in practice when the transfusion need is urgent. Currently, anti-IgA assays are performed most commonly using a passive hemagglutination assay,17 which is a technically challenging, time-consuming method available only at a handful of reference laboratories. Alternative methods of measuring anti-IgA include flow cytometry,18 solid-phase immunoradiometric assays with IgA coupled to microcrystalline cellulose,19 or enzyme immunoassays with IgA-coated microplates,20 none of which has become widely available due to a variety of factors, including requirement for costly instrumentation, technical expertise, and labor-intensiveness. The end result is that in real-life practice, IgA-deficient products are often requested for patients with a questionable diagnosis of IgAD, yet the clinical urgency precludes further diagnostic testing. Hence, clinicians and blood bankers face the dilemma of either procuring and issuing rare products when the clinical necessity is uncertain, or withholding transfusions until a time-consuming investigation can be completed, thus placing the patient at risk.

It must also be noted that the clinical significance of anti-IgA is not clear. Severe IgA anaphylactic reactions are rare events with only 1.3 occurrences per million blood products transfused according to one estimate.22 Yet, IgAD is a relatively common disorder, and depending on the sensitivity of the assay,28 to 53 percent11 of blood donors with severe IgAD (<0.05 mg/dL) also have detectable anti-IgA. The prevalence of anti-IgA is even higher in patients with autoimmune diseases such as juvenile rheumatoid arthritis (77%) or systemic lupus erythematosus (100%).23

Clearly, most detectable anti-IgA do not mediate anaphylactic transfusion reactions. The positive predictive value of anti-IgA is low, especially in a patient without history of prior reactions or nonsevere forms of IgAD. Detection of anti-IgA, at least by the current reference method of passive hemagglutination, likely overestimates the risk of anaphylactic reactions8 and may commit many patients to transfusion of IgA-deficient components unnecessarily. Currently we have no means to predict the clinical significance of anti-IgA in individual patients, although it is likely that antibodies with low titers or limited specificities are not as significant.

In this issue of TRANSFUSION, Brown and colleagues24 evaluated assays manufactured by DiaMed AG, Switzerland, to detect anti-IgA and IgAD. The tests utilize a standard particle-gel immunoassay format, or gel card technology, which was first described by Salama and colleagues25 in 2001. These tests generated results that were reasonably sensitive and showed good correlation with the standard reference methods and have the important advantages of being inexpensive, simple, fast to perform, and in a format familiar to many transfusion service laboratories. Requirement for additional instrumentation and user training would be limited. Therefore, this technology has the potential of being more widely adopted by blood bank laboratories and improving the availability and turn-around time of these assays. When correlated with the reference method for anti-IgA detection, the DiaMed anti-IgA assay correctly identified 6 patients with high-titer anti-IgA and severe IgAD, while most samples (16 of 18) with low-titer (≤128) anti-IgA gave negative results. Whether this apparently higher threshold of anti-IgA detection means improved specificity and ability to predict individuals at risk for IgA anaphylactic reactions remains to be seen. Further studies, including patients with prior anti-IgA-mediated anaphylactic reactions are needed to better define features of antibodies that are clinically important. The widespread use of IgAD and anti-IgA assays may also allow us to establish the true incidence of IgA anaphylactic transfusion reactions. Hopefully, with the increasing availability of such assays, and correlation of accumulated laboratory and clinical data, these goals can be accomplished in the near future.

Readily available gel card assays for IgAD and anti-IgA will serve as useful screening tests to evaluate requests for IgA-deficient products and exclude IgAD as the underlying cause for previous transfusion reactions. A negative IgAD screening test or anti-IgA result provides tremendous reassurance when IgA-deficient products are not available and virtually eliminates IgAD and anti-IgA as the cause for previous anaphylactic transfusion reactions. A positive result allows us to better recognize and manage true cases of IgA anaphylactic reactions and identify individuals who may be at risk for such reactions in the future.
Most importantly, the rapid turnaround times of these assays will likely facilitate timely provision of appropriate blood components to the patients being evaluated and ultimately contribute to better patient care.

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