

How I manage patients suspected of having had an IgA anaphylactic transfusion reaction

Transfusions of plasma-containing blood components may be associated with a variety of allergic-type reactions, ranging from a few hives to life-threatening laryngospasm or anaphylaxis. In the latter case, the possibility of anti-IgA-mediated anaphylaxis is often included in the differential diagnosis, but diagnostic and therapeutic options are limited. Testing for anti-IgA is available in only a few reference laboratories and supplies of frozen IgA-deficient plasma are in limited supply. Below, I offer an approach to the management of patients in this clinical situation for the new **TRANSFUSION** feature series "How Do I...?"

PATIENTS WITH A RECENT, REMOTE, OR DOCUMENTED HISTORY OF ANAPHYLAXIS AND/OR IgA DEFICIENCY

There are, essentially, three pertinent scenarios:

1. Patients who *just had* an anaphylactic or anaphylactoid transfusion reaction, which is reported to the transfusion service with the question "What do we do now?" and the statement "I need to (continue to) transfuse this patient." Based on the clinical history, a diagnosis of IgA deficiency is considered possible. The need for transfusion is urgent. These patients may or may not have history of prior blood transfusions or transfusion reactions.
2. Patients who have a history of a severe "anaphylactic" reaction, but either there was no specific laboratory follow-up or clinical details of the prior reaction are vague. As above, a diagnosis of IgA deficiency is being considered, but the need for resuming transfusion is not urgent.
3. Patients with a history of a severe anaphylactic transfusion reaction and a laboratory-confirmed diagnosis of IgA deficiency (with or without the presence of anti-IgA).

The different urgencies for resuming transfusions in each of these scenarios require different approaches, and the therapeutic options involve different risks of precipitating another adverse reaction.

IgA DEFICIENCY

Relative IgA deficiency, defined as a plasma IgA concentration that is less than the laboratory's reference range (<5 mg/dL in most laboratories), occurs in approximately 1:500 individuals. Such persons may experience symptoms of immune deficiency, but do not, necessarily, have *absolute* IgA deficiency (<0.05 mg/dL). Persons with absolute IgA deficiency may form class-specific alloanti-IgA, presumably, IgE anti-IgA. Such persons are at risk of an anti-IgA-mediated transfusion reaction (IgA anaphylaxis). Persons with normal or decreased concentrations of plasma IgA have been reported to have had adverse transfusion reactions attributed to subclass-specific anti-IgA1 or -IgA2. These are rare and unconfirmed events. IgA anaphylaxis has been reported to occur after the recipient's first blood transfusion.

INCIDENCE

There is no reliable estimate of the incidence of IgA anaphylactic transfusion reactions, because of nonstandardized diagnostic criteria and a lack of laboratory-based follow-up for most severe allergic-type transfusion reactions. There are at least 40 published case reports and numerous unpublished observations of severe IgA anaphylactic or anaphylactoid reactions in transfusion recipients. Most of these reports are more than 20 years old and may include some misdiagnosed cases of transfusion-related acute lung injury (TRALI) or other subsequently recognized causes of severe generalized transfusion reactions (see below).^{1,2}

DIAGNOSIS

Diagnostic criteria for IgA anaphylaxis are not well defined, and the conventional passive hemagglutination assay (PHA) used to detect anti-IgA is highly nonspecific. When the same anti-IgA assay that is used to diagnose reactions in *patients* was used in a program that screened 32,376 healthy blood *donors* for a registry of IgA-deficient donors, 1 in 1200 donors was found to be IgA-deficient (<0.05 mg/dL) with anti-IgA.³ This number of random healthy persons who fulfill the laboratory criteria that are used conventionally to confirm a clinical diagnosis of an IgA-related transfusion reaction greatly exceeds the observed incidence of anaphylactic reactions in patients receiving transfusions.

More than 75 percent of the case reports of IgA anaphylactic transfusion reactions were published before 1985 when TRALI was first recognized.^{2,4} Since 1985, an increasing proportion of acute generalized transfusion reactions with shortness of breath have been recognized to be due to TRALI.⁵ It is reasonable to speculate that some undiagnosed cases of TRALI in the 1970s and 1980s were misdiagnosed as IgA-related anaphylaxis. Other acute generalized transfusion reactions that were not recognized at the time when most case reports of IgA anaphylactic transfusion reactions were published include allergies to latex, antibodies to certain other serum proteins, and soluble allergens or donor-derived cytokines in transfused components.^{2,6}

None of 40 case reports of IgA anaphylactic transfusion reactions identified by computerized library searches attributed the immediate cause of death to anaphylaxis. The only published report of a fatality that we found was that of a 57-year-old man with a normal concentration of serum IgA, a low-titer "limited specificity" anti-IgA, and an autopsy report that attributed the cause of death to atherosclerotic heart disease, not anaphylaxis.⁷ Finally, a sense of the nonspecificity of diagnostic criteria for IgA anaphylactic transfusion reactions may be derived from a review of the results of testing blood samples referred to the American Red Cross National Reference Laboratory. Of 359 serum samples referred between 1978 and 1995 from patients with suspected diagnoses of IgA anaphylactic transfusion reactions, only 17.5 percent contained an IgA antibody of any serologic specificity.¹

In summary, the limitations of clinical diagnosis, together with the problem of nonspecific laboratory assays for anti-IgA, may result in overdiagnosis of IgA anaphylactic transfusion reactions. Scrutiny of the details of prior IgA anaphylactic transfusions may reveal that the diagnosis was considered more as a precaution than as the result of a well-documented clinical event confirmed by a laboratory finding of absolute IgA deficiency and anti-IgA.

APPROACH

1. Patients who just had an anaphylactic or anaphylactoid reaction, which is being reported to the transfusion service with the question "What do we do now?" and the statement "I need to transfuse this patient."

Ideally, a rapid laboratory test for IgA⁸ or anti-IgA⁹ could be used in an algorithm to exclude an IgA anaphylactic reaction when there is an urgent need to resume transfusions and the etiology of a prior anaphylactic reaction is uncertain. The particle gel immunoassay for anti-IgA⁹ is a promising new test that has been developed for this function, but it requires further clinical correlation before its pivotal role in the diagnosis of IgA anaphylaxis can be determined. In the absence of a rapid test for

anti-IgA, the patient's plasma should be tested for IgA concentration using a pretransfusion sample, that is, a sample that was obtained before *any* transfusions. Post-transfusion samples may contain some passively transfused IgA and can give a false-positive result. Many hospital laboratories can perform a test for IgA by nephelometry within 45 minutes. A result indicating the presence of any IgA rules out absolute IgA deficiency, which for practical purposes, excludes the likelihood of an anti-IgA-mediated anaphylactic reaction. Having excluded IgA anaphylaxis, that is, a *recipient*-related cause, a *unit*- or *donor*-related cause for the adverse event becomes more likely. Careful, controlled, and monitored transfusions may be resumed.

If timely screening for plasma IgA content cannot be performed or the result suggests a decreased, but not absolute deficiency of IgA, the recommended options are: 1) careful, controlled, and monitored transfusion with standard blood components; 2) transfusions of washed red blood cells (RBCs) or platelet (PLT) components; or 3) attempting to obtain blood components from known IgA-deficient donors.

Controlled transfusion of standard components.

Given the uncertainty that transfusing conventional blood components to a person with a history of an IgA anaphylactic reaction will result in a recurrent severe generalized reaction, I transfuse conventional plasma-containing blood products to patients if the indication for transfusion is urgent and unequivocal. Such transfusions are administered in-hospital, with constant monitoring, and with personnel and supportive resources for immediate treatment of a severe generalized reaction, if necessary.¹⁰ All blood components transfused in this scenario should be leukoreduced to minimize the possibility of a non-IgA-related, but otherwise allergic-type, reaction. Our hospital's blood supplier provides leukoreduced PLT and RBC components, but the procedure separates plasma from whole blood before leukoreduction filtration. For this reason, we use and recommend a bedside leukoreduction filter to remove residual white blood cells or fragments from plasma in this scenario (LPS high-efficiency leukoreduction filter for plasma, Pall Biomedical, Inc., East Hills, NY).

An alternative to this approach, although presently no longer feasible in the United States, is transfusion of pooled, solvent/detergent (S/D)-treated plasma (Plas+SD; American Red Cross). We reported the successful outcome of this approach in a patient with a prior history of repeated "anaphylactoid reactions" to plasma-containing blood products, who was IgA-deficient (<0.05 mg/dL) with anti-IgA2 ("limited specificity" antibody) by PHA.¹¹ The rationale for selecting S/D plasma is that filtering and other processing of pooled plasma during manufacture decrease the content of fragments of cellular elements that may be present in plasma and may

cause allergic-type reactions, unrelated to IgA. This patient subsequently tolerated an infusion of conventional intravenous immune globulin (IVIG; 1 g/kg) that contained IgA (720 µg/mL). The manufacturer has voluntarily withdrawn Plas+SD from distribution in the United States, but the option of using a processed, pooled plasma product should be considered, if another becomes available.

Washed RBC and PLT components. Protocols are available for washing RBC or PLT components to remove residual plasma before transfusion in recipients who are at risk for IgA anaphylactic transfusion reactions.¹² Many blood centers have procedures that use as many as five wash steps and decrease the concentrations of albumin and immunoglobulins by more than 95 percent. In patients for whom urgent transfusion of cellular components is needed, regardless of the degree of certainty of the diagnosis, this approach is less risky than transfusing conventional blood components.

Components from IgA-deficient donors. Because known IgA-deficient blood donors are rare (see below), their components should be reserved for cases where the clinical suspicion of recurrent and severe reactions is high. Also, these units require additional time to locate and acquire and, thus, they are of limited use in urgent circumstances.

2. Patients who have a past history of a severe anaphylactic reaction, but either there is no diagnostic (laboratory) follow-up or the clinical diagnosis is not known. As above, the diagnosis of IgA deficiency is being considered, but the need for resuming transfusions is not urgent.

A test for plasma IgA concentration should be performed for persons who did not recently receive transfusion. If the result indicates the presence of any IgA, that person cannot form a class-specific alloanti-IgA and an IgA anaphylactic transfusion reaction is excluded. Alternatively, if the history and/or laboratory report of IgA deficiency support the diagnosis of an IgA anaphylactic reaction, although as yet unconfirmed by the result of a test for anti-IgA, the recommended approach is to wash RBC and PLT components (see above) or locate components from an IgA-deficient donor.

Components from IgA-deficient donors. Plasma or PLTs collected from known IgA-deficient donors are available in certain community blood centers or via the American Rare Donor Program (Philadelphia, PA; 215-451-4900; 24 hr/7 days). Also, donor registries with lists of IgA-deficient donors have been established in Canada, Australia, Europe, and Asia.¹³ A low-IgA-content (1.2 µg/mL) IVIG product is available in the United States (Gammagard S/D IGIV 5 percent; Baxter Healthcare Corp., Glendale, CA).

3. Patients with a history of a severe anaphylactic transfusion reaction and a laboratory-confirmed diagnosis of IgA deficiency.

Recurrent episodes of IgA anaphylaxis are preventable if plasma or PLTs for subsequent transfusions are collected from IgA-deficient donors (<0.05 mg/dL)³ or if IVIG is administered with IgA-depleted products (<1.2 µg/mL).¹⁴ For this reason, the safest option is transfusing IgA-deficient blood components whenever transfusions are not urgent.

SUMMARY

In the absence of evidenced-based guidelines—and because patients with a history of an anaphylactic transfusion reaction may need an immediate decision concerning blood transfusion—I use the following principles to guide my approach. If time permits, I attempt to locate and transfuse IgA-deficient blood components. If a transfusion is needed urgently and IgA-deficient components cannot be supplied in time, I scrutinize the report of the IgA anaphylactic reaction because, in my experience, IgA anaphylactic reactions are frequently overdiagnosed. If a pretransfusion plasma sample can be located for IgA testing, a result indicating the presence of any IgA essentially excludes the likelihood that the prior reaction was mediated by alloanti-IgA. If the indication for transfusion is urgent and unequivocal, and if the history of a prior IgA anaphylactic transfusion reaction is equivocal, I transfuse conventional blood components in a well-monitored in-hospital setting. Decisions to transfuse in this situation are based on a determination that there is a greater risk to the patient by withholding transfusions, rather than transfusing urgently needed blood components.

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