

Review: IgA anaphylactic transfusion reactions.

Part II. Clinical diagnosis and bedside management

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In Part I, Dr. R.R. Vassallo addressed laboratory assays for IgA and anti-IgA, their application to defining the incidence of IgA-related transfusion reactions, and the provision of IgA-deficient blood products. Part II will address the clinical diagnosis of IgA anaphylactic transfusion reactions and bedside management. The viewpoint of this review is that IgA anaphylactic transfusion reactions are serious but uncommon events that must be distinguished from other acute generalized reactions that occur more commonly, for example, transfusion-related acute lung injury (TRALI). Subsequent transfusions in persons with a history of an IgA anaphylactic transfusion reaction should be safe and uneventful using either washed RBCs or platelets or plasma from IgA-deficient donors. Clinical diagnosis of IgA anaphylactic transfusion reactions must be confirmed by laboratory testing for anti-IgA before unnecessarily committing a patient to a lifelong requirement for these specialized blood components if blood transfusion is needed in the future.

Definitions

Conventionally, IgA anaphylactic transfusion reactions are defined as anaphylaxis occurring within 1 hour of transfusing a plasma-containing blood product in a patient who is IgA deficient (< 0.05 mg/dL) and whose plasma contains anti-IgA.¹ In addition, there are case reports of persons with normal or low concentrations of IgA whose transfusion-related anaphylactoid reactions have been attributed to IgA antibodies of limited serologic specificity (i.e., IgA subclass antibodies). Published case reports of IgA anaphylactic transfusion reactions use the terms *anaphylaxis* and *anaphylactoid*, which require additional definitions, as follows.

Anaphylactic reactions

Anaphylaxis is a generalized, immediate, type I hypersensitivity reaction caused by IgE-mediated activation and degranulation of mast cells and basophils.² Typical reactions are unexpected, explosive, and catastrophic, and they may be fatal. Usually, signs and symptoms are cutaneous (hives), pulmonary (wheezing), cardiovascular (hypotension), and/or gastrointestinal (diarrhea). However, many different presentations have been reported (Table 1).

Table 1. Signs and symptoms of IgA anaphylactic reactions

Cutaneous:	Urticaria, flushing, hives, rash, angioedema
Respiratory:	Wheezing, dyspnea, bronchospasm, stridor
Cardiovascular:	Hypotension, shock, loss of consciousness, cardiac arrhythmia, syncope, cardiac arrest
Gastrointestinal:	Abdominal cramps, diarrhea, vomiting

Anaphylactoid reactions

An anaphylactoid reaction is clinically similar, but not mediated by IgE.² Since nearly all published case reports of IgA anaphylactic transfusion reactions have been confirmed by laboratory tests that do not specifically identify *IgE* anti-IgA, most reported cases are, technically, anaphylactoid reactions. In the first published report, Vyas and colleagues classified IgA transfusion reactions into two groups: (1) anaphylactic reactions associated with severe clinical symptoms, class-specific anti-IgA, and absence of plasma IgA and (2) anaphylactoid reactions associated with milder clinical reactions, anti-IgA of limited serologic reactivity, and normal plasma concentrations of IgA.³ Of the 40 case reports of IgA-related transfusion reactions that have been published in journal articles,

only eight are classified by their authors as anaphylactoid.¹ Authors of case reports for IgA transfusion reactions generally use the terms anaphylactic (versus anaphylactoid) to distinguish severe (versus milder) reactions or class-specific (IgA) (versus limited-specificity anti-IgA1 or -IgA2) antibodies. The conventional distinction between IgE and IgG or IgM anti-IgA is not apparent when reading published case reports of IgA anaphylaxis. Given this lack of precise definitions in published case reports, we will use the designation *IgA anaphylactic transfusion reactions* in this review to include all acute generalized reactions attributed to anti-IgA.

Differential Diagnosis

The first report of an IgA anaphylactic reaction was published in 1968, prior to recognition of several other acute generalized transfusion reactions (Table 2). TRALI, the most pertinent acute transfusion reaction to be distinguished from IgA anaphylaxis, was first recognized in 1985,⁴ i.e., after more than 75 percent (31/40) of the case reports of IgA anaphylaxis had already been published.¹ Other transfusion-related anaphylactic reactions that were recognized after most cases of IgA anaphylaxis were published include anti-Rga (1984),⁵ anti-Cha (1992),⁶ anaphylactic reactions to HLA-incompatible platelets (1993),⁷ and IgE-mediated anti-haptoglobin (2000).⁸ Passively transfused drugs (penicillin, aspirin)^{9,10} or drug antibodies (anti-cephalosporin)¹¹ have been reported to cause anaphylactic reactions. As the number of other potential causes for severe generalized transfusion reactions increases, it becomes apparent that some clinical diagnoses of IgA anaphylactic reactions, including early published case reports confirmed by weakly reacting IgA antibodies of limited specificity,

may have been misdiagnoses. This personal impression is supported by our experience testing blood samples from patients with suspected IgA anaphylactic reactions that were referred to the American Red Cross National Reference Laboratory. Of 359 samples only 65 (18.1%) contained an IgA antibody of any specificity.¹² Thus, 81.9 percent of 359 anaphylactic transfusion reactions that were suspected, clinically, to be anti-IgA anaphylactic transfusion reactions were, in fact, caused by other factors.

ABO hemolytic transfusion reactions

The differential diagnosis of an immediate systemic reaction in a person receiving a RBC transfusion should begin by excluding a possible ABO-related acute hemolytic transfusion reaction. Prompt diagnosis and aggressive management can reduce formerly high fatality rates of ABO hemolytic reactions to (only) 10 percent.¹³ A clerical check to verify positive identification of the blood sample used for compatibility testing, the patient, and the blood component should quickly resolve this issue. The absence of a pink or red color (reflecting hemoglobin monomers or dimers) in samples of the patient's posttransfusion urine or plasma excludes a diagnosis of an acute hemolytic transfusion reaction.

TRALI

TRALI is recognized with increasing frequency and is now the most frequent cause of fatal transfusion reactions reported to the U.S. Food and Drug Administration.¹⁴ Like IgA anaphylactic transfusion reactions, TRALI presents with predominantly pulmonary findings, e.g., shortness of breath, cyanosis, and hypoxia.^{14,15} In contrast to the predominance of upper airway signs (stridor, bronchospasm) in anaphylactic reactions, the clinical findings in TRALI are more typical of noncardiogenic pulmonary edema. Fever is present in most cases of TRALI, whereas fever is uncommon in IgA anaphylactic transfusion reactions.

Bacterial contamination and endotoxemia

The sudden onset of hypotension and shock during the first few minutes of a blood transfusion may raise the question of an IgA anaphylactic transfusion reaction. The presence of rigors and fever, sometimes over 40°C, should direct diagnostic efforts toward bacterial contamination and sepsis.¹⁶

Table 2. Other transfusion-related acute generalized reactions that may be pertinent in the differential diagnosis of IgA anaphylaxis

ABO hemolytic reactions
TRALI ^{4,15}
Bacterial contamination/endotoxemia
Angiotensin-converting enzyme inhibitors ¹⁷
Circulatory overload ⁸
Anti-Rg ⁵
Anti-Ch ⁶
HLA-incompatible platelets ⁷
Anti-haptoglobin ⁸
Passively transfused allergens ⁹⁻¹¹
Coincidental exposure to allergens (food, medication, latex, others)

Angiotensin-converting enzyme (ACE) inhibitors

Patients who are being treated with ACE inhibitors for hypertension or heart failure may develop "anaphylactoid" reactions (flushing and hypotension) during albumin infusions.¹⁷ The reaction is believed to result from the presence of prekallikrein activator in albumin products, which converts prekallikrein to bradykinin, a vasoactive peptide. ACE inhibitors cause the accumulation of bradykinin. The temporal association of an infusion of albumin, together with the absence of hypoxia or other pulmonary symptoms, points away from an IgA anaphylactic reaction.

Circulatory overload

An infant or elderly patient who develops acute hypoxia during a blood transfusion should be evaluated first for possible circulatory overload due to hypervolemia.¹⁸ Rales and other signs of pulmonary congestion exclude IgA anaphylaxis.

Coincident exposure to allergens

The visual image of a patient in anaphylaxis who is receiving a blood transfusion logically directs the differential diagnosis to the blood product. Nevertheless, that patient may be experiencing a coincidental acute IgE- (or non-IgE-) mediated reaction to medication, food, or exercise.² Latex gloves and certain other latex-containing hospital appliances are recognized causes of anaphylactic reactions.² However, awareness of the risk that latex presents to patients and hospital personnel has greatly reduced the presence of latex-containing products in patient care areas.

Bedside Management

There are two principal aspects of the management of patients with IgA anaphylactic reactions: (1) treatment of the acute clinical event and (2) selection of blood products for subsequent transfusions.

Treating IgA anaphylactic transfusion reactions

Effective management of an IgA anaphylactic transfusion reaction begins, proactively, by establishing a hospital policy that ensures all transfusions will be administered in clinical areas where appropriate medications, equipment ("crash cart"), and trained personnel are readily available. A detailed list of medications and equipment may be found in standard textbooks.² Minimum equipment includes an oxygen source and masks, needles and tubing for intravenous fluids, defibrillator, suction apparatus, laryngoscope,

endotracheal tubes, nonlatex gloves, and an Ambu-bag. The medications should include epinephrine (aqueous, 1:1000), injectable diphenhydramine, injectable corticosteroids, dopamine, and atropine. Specific treatment depends on the prominence of individual clinical findings. First, the blood transfusion must be discontinued and intravenous access maintained with 0.9% sodium chloride for administration of parenteral medications. For shortness of breath, oxygen via a face mask should be started and a decision made whether or not intubation (endotracheal tube) is needed. Epinephrine is the most effective medication for relieving the acute symptoms of anaphylaxis. The exact dose and route depend on the patient's circulatory status. Often anaphylaxis has a biphasic course, i.e., after the initial episode has resolved following treatment there is a recurrence of acute symptoms requiring re-treatment within the next 2 hours. Depending on the severity of the initial reaction, patients should be observed in an intensive care setting for 2 to 24 hours after resolution of all symptoms.

Subsequent transfusions: IgA anaphylaxis suspected, but not confirmed

The above scenario describes an acute generalized reaction which occurred during a blood transfusion that may (or may not) have been an IgA anaphylactic transfusion reaction. If additional transfusions are required in such a situation, they may be needed before laboratory testing for anti-IgA can be completed. A similar situation occurs when a patient needing an urgent blood transfusion gives a medical history of a prior transfusion-related anaphylactic reaction, but testing for anti-IgA was not performed or the results are not available. In this situation, the safest blood components are washed red blood cells¹⁹ and platelets or plasma from known IgA-deficient donors.²⁰ If a platelet transfusion is required before an IgA-deficient component can be supplied, platelets may be washed, although considerable skill and experience is required to avoid platelet clumping, activation, and loss of platelets.¹⁹ If FFP is urgently required before IgA-deficient components can be supplied, withholding transfusions may create a greater risk to the patient than initiating a slow transfusion of standard FFP in a carefully monitored nursing unit. Since anti-IgA was detected in only 18.1 percent of cases of suspected IgA anaphylaxis (see above), there is a reasonable possibility that anti-IgA is not present and subsequent

transfusions will be uneventful. While such an approach is not without risk, we are unaware of any published case report describing a fatality that was directly caused by an IgA anaphylactic transfusion reaction.^{1,21,22} The only published report of a fatal IgA anaphylactic transfusion reaction that we have been able to locate is that of a 57-year-old man with a normal concentration of plasma IgA, a low titer anti-IgA of limited serologic specificity (titer = 64), and an autopsy report of hemorrhagic pulmonary edema, focal severe coronary artery disease of the left anterior descending artery, and focal early ischemic change in the anterior wall of the left ventricle.¹⁰

Subsequent transfusions: prior IgA anaphylactic reaction confirmed by anti-IgA

The management of a patient whose history of one or more anaphylactic transfusion reactions has been confirmed by a test for plasma anti-IgA is straightforward in principle and difficult in practice. In principle, subsequent transfusions of blood products that are deficient in IgA should be safe and uneventful. In practice, such blood products are not readily available in hospital transfusion services or in most blood centers. If plasma or platelets are needed, and if time allows, the first and safest strategy should be an effort to locate IgA-deficient components via the community blood center. Certain community blood centers have lists of donors who have been tested and confirmed to be IgA-deficient and, using emergency release procedures, the centers may collect and supply such components in an urgent situation. In addition, lists of IgA-deficient blood donors have been established in the United States, Canada, Australia, and certain countries in Europe and Asia.^{20,23} In the United States, IgA-deficient blood components may be requested via the American Rare Donor Program, Philadelphia, Pennsylvania (215-451-4900; 24 hours/7days). A low-content IgA IVIG product is available in the United States (Gammagard S/D IGIV 5%; Baxter Healthcare Corporation, Glendale, CA). Standard RBCs may be transfused after automated washing to remove residual IgA-containing plasma.¹⁹ Of course, any RBCs that become available if whole blood is collected from IgA-deficient donors for plasma or platelets may be transfused without washing.

Lastly, if severe bleeding with a coagulopathy occurs in a patient with IgA deficiency and anti-IgA, and platelets or FFP from an IgA-deficient donor is not readily available, an "off-label" infusion of recombinant

activated coagulation factor VII (rFVIIa; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) may be a reasonable alternative. Case reports describe efficacy of infusions of rFVIIa in certain systemic bleeding disorders where platelets²⁴ or FFP²⁵ would be indicated. While none of these case reports relate to IgA-deficient patients specifically, rFVIIa does not contain IgA and, therefore, should not precipitate a recurrent anaphylactic reaction.

Summary

Numerous published case reports of IgA-related anaphylactic transfusion reactions (1968–present) alert us that certain IgA-deficient persons are at risk for acute generalized transfusion reactions, presenting with severe shortness of breath. However, such IgA anaphylactic transfusion reactions are uncommon, and the majority of clinical diagnoses are not confirmed by detection of anti-IgA in the patient's plasma. The recognition of other transfusion-related acute generalized reactions in recent years requires expanding the differential diagnosis for such events to include other possible diagnoses, most importantly TRALI. Clinical diagnoses of IgA anaphylactic transfusion reactions should be followed up promptly by testing for anti-IgA. Failure to follow up a clinical diagnosis by testing for anti-IgA will complicate management of any future blood transfusions and potentially commit the patient to a lifelong requirement for highly specialized IgA-deficient blood products.

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