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Anaphylactic Reactions to Blood Transfusions: Focus on Alpha-Gal Syndrome

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H&O What is alpha-gal syndrome?

CG Alpha-gal syndrome is an immunoglobulin E (IgE)–mediated allergy to galactose-α-1,3-galactose, a carbohydrate found in meat from nonprimate mammals and in some products derived from mammals. The syndrome typically develops weeks or months after a bite by an infected lone star tick. Reactions can include hives, gastrointestinal symptoms such as abdominal pain and diarrhea, anaphylaxis, and even loss of consciousness.

Alpha-gal syndrome is an unusual allergy for 2 reasons. First, it is the first identified major allergy to a carbohydrate epitope rather than a protein. Second, the allergic reaction is delayed. Unlike anaphylaxis due to the consumption of peanuts, which develops immediately, this allergic reaction appears 2 to 6 hours after the ingestion of meat. Many people with alpha-gal syndrome do not know they have it because of this delay. Two of my own patients had no idea they had alpha-gal syndrome before they collapsed and were brought to an emergency department. One patient collapsed twice before he associated his reaction with some pork dumplings he had eaten.

H&O How is alpha-gal syndrome diagnosed?

CG The diagnosis is determined by obtaining a detailed history of tick bites and dietary exposure, along with blood testing for alpha-gal–specific IgE. Alpha-gal IgE positivity alone is not sufficient because sensitization can occur without clinical disease. Obtaining a complete patient history is key. The American Gastroenterological Association has prepared an excellent guide on how to diagnose alpha-gal syndrome because some patients present with gastrointestinal symptoms only.[1]

H&O What blood products present a risk to patients with alpha-gal syndrome?

CG The strongest signals so far have been with group B and possibly group AB plasma, platelets, and cryoprecipitate when they are given to non-B recipients, particularly those in group O. Although current reports do not suggest the same level of concern with red blood cells, we have seen 2 cases of reactions associated with transfusions of group O red blood cells here at Georgetown. One of these patients is described in our case series on anaphylactic transfusion reactions in 3 patients in 2 hospitals in Washington, DC, from November 2022 to February 2023[2]; this patient experienced 2 reactions to plasma and one to red blood cells. Theoretically, if whole blood was collected from a donor who had eaten meat 2 to 6 hours before the donation, the blood could contain glycolipids carrying the alpha-gal epitope regardless of the donor's blood group and cause a reaction in a patient with group O blood and IgE to alpha-gal.

H&O Which patients are at highest risk for transfusion reactions?

CG Patients at highest risk are non–group B recipi-

ents—especially group O recipients—who have known or possible alpha-gal syndrome, a history of tick exposure, or prior reactions to mammalian meat. Having group B blood may be relatively protective against alpha-gal syndrome. Our case series also suggests that patients with animal allergies may be at higher risk for severe reactions.[2]

> Alpha-gal–mediated reactions to blood transfusions are a poorly publicized phenomenon.

H&O Should blood banks be screening or labeling blood products for alpha-gal risk factors?

CG Screening blood products for alpha-gal risk factors is not currently recommended, but it may become necessary if we begin to see reactions to group O red blood cells or other components. There is already a precedent for preventing recipient exposure by donor history rather than component testing. Anaphylactic reactions caused by IgA-positive blood products in patients with IgA deficiency was first described in the 1960s. In response, the American Red Cross has a created a large registry of IgA-deficient plasma donors for use when plasma is administered to IgA-deficient recipients who have had anaphylactic reactions. Given that anaphylactic reactions caused by alpha-gal syndrome are more common than those caused by IgA deficiency, it would be reasonable to create a registry of vegetarian donors with blood group O, or just inquire about dietary history before donation, to prevent reactions in patients with alpha-gal syndrome. We have had experience with a patient with a fish allergy for whom donors were recruited who agreed not to eat fish in the week before donation.

H&O How can the risks of transfusions be minimized?

CG The first step is to avoid unnecessary transfusions. Many transfusions are prophylactic, and the risk-vs-benefit equation changes in a patient with alpha-gal syndrome. Clinicians need to document alpha-gal syndrome clearly, alert the blood bank in advance, and use only non-B plasma or platelets. All transfusions in patients with alpha-gal syndrome should be started slowly, with close observation, and stopped immediately if a reaction is suspected. Fast transfusions should be avoided.

We normally avoid the use of group B blood products unless the recipient has group B blood, but sometimes they are the only products we have on the shelf. In that case, I recommend that patients be screened for alpha-gal syndrome before transfusion. If the patient has recently eaten red meat and had no problems, we do not need to suspect alpha-gal syndrome. But if the questioning raises points of concern, we need to test the patient for alpha-gal syndrome before transfusion. If the test result is positive, we may just need to wait several hours for the right blood product.

H&O What signs and symptoms develop during a transfusion reaction?

CG The signs and symptoms are the same as those of a classic anaphylactic reaction to a bee sting: pruritus, hives, angioedema, flushing, abdominal pain, nausea, vomiting, diarrhea, dyspnea, hypotension, dizziness, and loss of consciousness.[3] In classic food-triggered alpha-gal syndrome, the symptoms often begin 2 to 6 hours after exposure, but transfusion-related symptoms occur immediately during the transfusion and appear identical to those of other acute allergic/anaphylactic transfusion reactions. We do not see mild symptoms such as isolated diarrhea with anaphylactic transfusion reactions; if the patient is going to have a reaction to a blood product, it will be a standard anaphylactic transfusion reaction.

H&O How does an alpha-gal–mediated reaction differ from other types of transfusion reactions?

CG Alpha-gal–mediated reactions present identically to the well-described entities of allergic and anaphylactic transfusion reactions. If the reaction manifests with predominantly respiratory symptoms, without a rash or urticaria, a serum tryptase level can be obtained within 2 hours after symptoms develop to support that the reaction is anaphylaxis and not a respiratory reaction like transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), or transfusion-associated dyspnea (TAD).

All allergic and anaphylactic reactions should be evaluated by obtaining the patient's history of allergies and previous transfusions. If a patient has tolerated other transfusions previously, a workup for an IgA deficiency is unlikely to be fruitful. Because we are in a high-incidence area and alpha-gal syndrome had not been previously diagnosed in all 3 of the patients described in our case series,[2] I maintain a very low threshold of suspicion for ordering an alpha-gal/meat allergy panel on all our patients with moderate to severe allergic reactions. This low threshold allowed us to discover the diagnosis of alpha-gal syndrome in a second patient with a reaction to red blood cells.

H&O How are these reactions managed?

CG The management of alpha gal–mediated reactions is the same initially as that for other suspected transfusion reactions. We stop the transfusion, assess the patient, notify the transfusion service, and treat according to severity. Treatments include antihistamines for mild reactions and epinephrine plus supportive care for anaphylaxis; supportive care may involve intubation or admission to the intensive care unit. If alpha-gal syndrome is suspected, future avoidance of implicated plasma-containing products is prudent while the evaluation proceeds.

H&O What do we still not understand about alpha-gal syndrome in the transfusion setting?

CG Major gaps include the true incidence of reactions to red blood cells or other group O components, and what may cause these reactions. I suspect that risk originates from the ingestion of meat or possibly the inhalation of animal dander by the donor, but the accuracy of this idea has not been established. We also do not know whether the most clinically relevant alpha-gal epitopes in blood components are present on cell membranes and cell membrane fragments, plasma proteins, or both.

H&O Is there anything you would like to add?

CG Alpha-gal–mediated reactions to blood transfusions are a poorly publicized phenomenon, and I would like to get the word out. We had 2 deaths due to anaphylactic reactions at Georgetown, and then for the past 3 years no other cases occurred after we stopped transfusing group B components to group O recipients. We also added documentation of alpha-gal syndrome to our blood bank electronic medical record at MedStar more than a year ago, which should become the standard at all institutions.

A French group recently published data on a cohort of 59 patients with severe allergic transfusion reactions that supported alpha-gal sensitization as an important factor in major ABO-incompatible transfusion reactions.[4] I hope that this study and others like it will increase awareness of this important and growing problem.

Disclosures

Dr Gilstad has no conflicts of interest to disclose.

References

1. McGill SK, Hashash JG, Platts-Mills TA. AGA clinical practice update on alpha-gal syndrome for the GI clinician: commentary. *Clin Gastroenterol Hepatol.* 2023;21(4):891-896.
2. Gilstad CW, Conry-Cantilena K, Zarpak R, Eder AF. An outbreak of anaphylactic transfusion reactions to group B plasma and platelets and its possible relationship to alpha-gal syndrome. *Transfusion.* 2023;63(10):1997-2000.
3. Hirayama F. Current understanding of allergic transfusion reactions: incidence, pathogenesis, laboratory tests, prevention and treatment. *Br J Haematol.* 2013;160(4):434-444.
4. de Chaisemartin L, de la Taille V, Nicaise-Roland P, et al. Severe allergic transfusion reactions to group B/AB plasma or platelets in group O recipients are linked to α-gal sensitization. *Blood.* 2026;147(25):3113-3117.