

Invited Commentary: Alpha-Gal Allergy: Tip of the Iceberg to a Pivotal Immune Response

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Published online: 13 August 2016
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Abstract The syndrome of delayed allergic reactions to the carbohydrate galactose-alpha-1,3-galactose (“alpha-gal”) has become increasingly recognized in allergy and immunology clinics regionally throughout the southeastern USA. Due to the increasing awareness of this unique food allergy, cases have been identified in the northeastern and central USA as well as in Central and South America, Europe, Asia, Scandinavia, and Australia. Clinically, alpha-gal allergy is characterized by reactions to non-primate mammalian meat (e.g., beef, pork, lamb) that occur 3–6 h following exposure. The IgE response to alpha-gal is thought to develop after tick bites and can result in the loss of tolerance to foods that have been safely consumed for years. Although the initial description of alpha-gal allergy in 2009 was limited to red meat, this epitope is now identified in an expanded number of products, medications and foods—both labeled and unlabeled. Moreover, we are beginning to recognize that alpha-gal food allergy is the tip of the iceberg for this immune response.

Keywords Alpha-gal · IgE · Red meat allergy · Delayed anaphylaxis · Anti-Gal · Tick bite and allergy

Implications of the immune response to galactose-alpha-1,3-galactose

Food allergy

Reactions to beef, pork, lamb, venison, goat, bison, and rabbit (as well as other sources of non-primate mammalian meat) have been described in patients who develop alpha-gal allergy. Clinical manifestations of alpha-gal allergy have been reviewed elsewhere; however, two specific points are important to note that were not appreciated at the initial description of the syndrome. First, cow’s milk and related dairy products can make significant contributions to the number of allergic reactions for many patients. Symptoms related to dairy are frequently reported to be gastrointestinal and, in keeping with the red meat reactions, the onset is delayed over 2 h. Clinical experience suggests that cow’s milk-based ice cream is the most frequent trigger for allergic reactions to food behind red meat. Second, patients who reported symptoms limited to gastrointestinal complaints are increasingly being identified. These patients report severe abdominal cramping often accompanied by an episode of diarrhea that appears to be unrelated to food consumption. In the absence of hives, itching, swelling, or even hypotension, it is difficult to suspect an allergic etiology. As such, numerous patients with similar histories have had a colonoscopy, endoscopy, or cholecystectomy when avoidance of red meat and dairy would have been sufficient.

Vaccines

Several common vaccines contain known amounts of gelatin, which is typically mammalian-derived. Published concentration of gelatin in vaccines is highest for MMR and live

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attenuated herpes zoster (Zostavax®). Of these two vaccines, herpes zoster has more impact on the adult alpha-gal allergic patient. Case reports and clinical experience of immediate allergic reactions to the herpes zoster vaccine in alpha-gal allergic patients have informed the frequent decision to delay or recommend against routine use of this gelatin-containing vaccine in patients with alpha-gal IgE. Although there have been reports of reactions to influenza vaccines that may contain gelatin, this seems to be rare and product-specific as the gelatin concentration may vary depending upon the manufacturer.

Heparin

Widespread use of heparin coupled with the relatively few reports of reactions among alpha-gal allergic patients suggests that clinical hypersensitivity is uncommon. However, since pharmaceutical-grade heparin is porcine (intestine) or bovine (lung) in origin the likelihood of alpha-gal being present is high. Heparin skin testing could be an appropriate screening mechanism for patients with alpha-gal IgE but this approach has not produced consistent results. The most likely factors that determine whether a reaction will occur may be the dose of heparin and the animal source. Of the reactions reported, many have been related to high-dose heparin associated with extracorporeal membrane oxygenation or other cardiac procedures. Variability in the source, processing and purity of heparin has been described and even led to over 80 deaths due to oversulfated chondroitin sulfate in 2007–8. Thus, a clinical reaction to heparin in an alpha-gal allergic individual may necessitate a high dose with a specific lot that is more heavily intestinally-derived (due to tissue distribution of alpha-gal)—which may explain the inconsistent skin test results with heparin. Nevertheless, heparin is routinely used throughout the healthcare system and this fact alone requires our increased awareness of the potential risks for patients with alpha-gal IgE.

Bioprosthetic Heart Valves

Bioprosthetic heart valves are commonly porcine in origin and this raises two primary issues. For patients with alpha-gal allergy, there is obvious concern that the valve will trigger an allergic reaction. In fact, this has been reported—as have bioprosthetic implants without reaction. One likely determining factor is the fixation used by the valve manufacturer as not all glutaraldehyde fixation processes guarantee complete removal of alpha-gal. A second concern is whether the presence of alpha-gal epitopes remaining on bioprosthetic heart valves could lead to premature valve destruction in patients with alpha-gal IgE (since IgE is pro-inflammatory). All immunocompetent humans produce IgM, IgA, IgG, and IgD against alpha-gal, so a wider issue may be whether *most* premature

bioprosthetic heart valve destruction is linked to the presence of alpha-gal epitopes on the valve. To this point, circulating alpha-gal IgG antibodies increase significantly within 10 days after bioprosthetic heart valve implantation.

Atherosclerosis

There is no clear reason why an IgE response to alpha-gal would affect atherosclerosis; however, the presence of other antibody isotypes directed against alpha-gal could mediate the uptake of lipid into macrophages. When we consume red meat, lipid from those animals will contain alpha-gal sugars which can be recognized and bound by IgG, IgM and IgD antibodies. The lipid-antibody complex can then be taken up through receptor-mediated endocytosis into macrophages. In fact, preliminary studies have found that anti-carbohydrate antibodies, including anti-alpha-gal, may represent a new class of risk factors that may be associated with presence of advanced atherosclerosis.

Inflammatory Bowel Disease

Production of IgM, IgG, IgA, and IgD antibodies that recognize alpha-gal appear to be stimulated in humans by our commensal gut flora. When alpha-gal deficient mice are raised in a sterile environment, these animals do not produce an anti-Gal response. Because of the dominant role of gut flora in the alpha-gal response, it has been hypothesized that patients with inflammatory bowel disease may display increased anti-Gal titers due to the chronically impaired mucosal gut barrier. In a small study, patients with Crohn's disease displayed increased anti-Gal IgA titers compared with healthy controls. Using similar rationale, we have seen success with a mammalian meat avoidance diet in adults thought to have irritable bowel syndrome.

Sero-Negative Lyme Disease

Diagnosis of Lyme disease is complicated by serologic tests that can frequently be negative and even Western blot bands that do not have universal standards. Patients with suspected Lyme disease may have a constellation of symptoms including fatigue, joint pain, and gastrointestinal distress in the setting of tick bites. Given the intersection of these symptoms and history with that of alpha-gal allergy, we have made use of a mammalian meat avoidance diet in patients with “sero-negative” Lyme disease. Several patients reported striking improvement and even resolution of chronic symptoms while avoiding alpha-gal-containing foods. Our assumption is that sero-negative Lyme disease in many cases is not Lyme disease but rather tick bite-induced intolerance of alpha-gal if not frank alpha-gal allergy. The association between tick bites

and an altered immune response will be a challenging but rewarding investigation in the future.

Conclusion

The immune response to galactose-alpha-1,3-galactose can include each antibody isotype. Recent studies from the seemingly disparate fields of oncology and tropical vector-borne disease have demonstrated the potential role for alpha-gal immune response to have prognostic significance in cancer survival and in the control of malaria transmission, respectively. Tick bite-induced alpha-gal allergy to red meat may have par-

ticular importance in elucidating otherwise idiopathic allergic reactions but this might well be the tip of the iceberg. The immune response to alpha-gal may have deeper implications, however, by bringing renewed attention to the biological importance of the galactose-alpha-1,3-galactose epitope.

Compliance with Ethical Standards

Conflict of Interest Dr. Commins reports personal fees from Genentech, grants from NIH, and personal fees from Up-To-Date.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.