Anaphylaxis to the Carbohydrate Side Chain Alpha-gal

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KEYWORDS

• Delayed anaphylaxis • Alpha-gal • Ticks • Red-meat allergy • Cetuximab

KEY POINTS

- In 2007, the monoclonal antibody cetuximab was causing severe hypersensitivity reactions during the first infusion in a region of the southeastern United States.
- Investigation of pretreatment sera established that they contained immunoglobulin (Ig) E against the oligosaccharide galactose-alpha-1,3-galactose (alpha-gal), which is present on the Fab of cetuximab.
- Alpha-gal is a blood group substance of nonprimate mammals.
- These IgE antibodies are also associated with delayed anaphylaxis to red meat (ie, to meat or organs of those animals that carry this oligosaccharide).
- There is now extensive evidence that the primary cause of these IgE antibodies is bites from the tick *Amblyomma americanum* or its larvae.

INTRODUCTION AND HISTORY

When Karl Landsteiner[1] first defined the ABO system, he also recognized a B-like substance on mammalian cells. At that time he reported that all immunocompetent individuals had agglutinating antibodies against this substance. Adsorption of these antibodies against rabbit red cells was part of the proof that rabbit cells can activate the alternate pathway of human complement.[2] This B-like substance is now known to be galactose-alpha-1,3-galactose (alpha-gal), which is structurally similar to the B blood group (**Fig. 1**).[3,4] This carbohydrate is a well-recognized immunologic barrier

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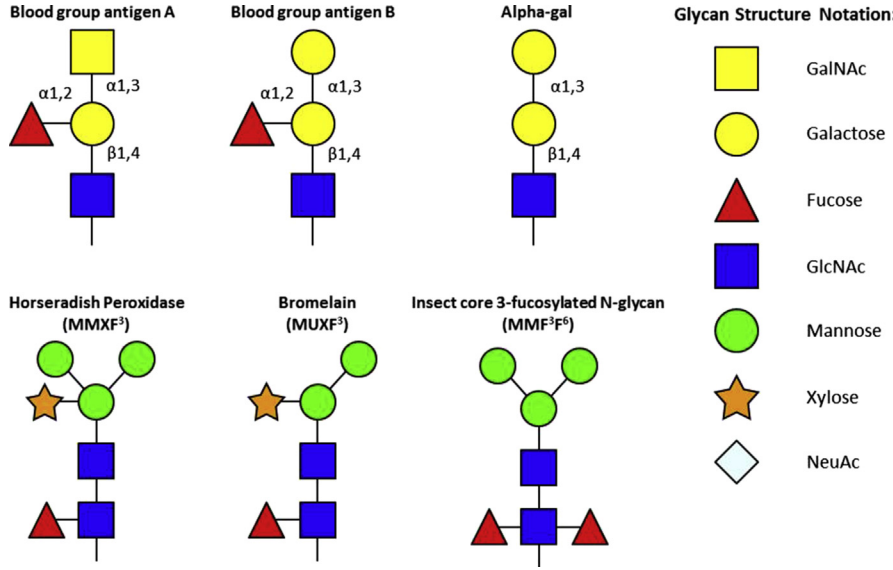

Fig. 1. Glycan structure of blood group antigens and alpha-gal contrasted with those of plant- or insect-related Cross reactive carbohydrate determinants. (*Adapted from* Commins SP, Platts-Mills TA. Anaphylaxis syndromes related to a new mammalian cross-reactive carbohydrate determinant. J Allergy Clin Immunol 2009;124(4):652–57.)

in xenotransplantation. Xenoreactive natural antibodies directed against the alpha-gal moieties on nonprimate mammalian tissue are often implicated in acute organ rejection. One way to circumvent this obstacle may be to raise transgenic organs in pig knockouts lacking the gene expressing alpha-(1,3)-galactosyl transferase, an enzyme inactivated in all primates.[5] It has also been suggested that the antibody response to alpha-gal is as much as 1% of the total immunoglobulin; however, more recent assays in our group suggest a low quantity of immunoglobulin (Ig) G antibodies.[6,7]

The story of IgE to alpha-gal starts in 2006 with 2 anaphylactic reactions to cetuximab in Bentonville, Arkansas, 1 of which was fatal. At the same time, there were 4 observations that were interesting but unexplained:

1. The monoclonal antibody (mAb) cetuximab was causing severe anaphylactic or urticarial reactions in up to 15% of patients treated in Tennessee and North Carolina but not in New York or Boston[8]
2. A patient aged 43 years reported 4 episodes of anaphylaxis, each of which started 4 hours after eating a hamburger (**Box 1**)
3. Sixty percent of the school children in a Kenyan village had serum IgE specific for cat extract, although there were no cats in the village and no relevant allergic symptoms[9]
4. The increasing deer population in rural and suburban Virginia had reached epidemic numbers

At that point, there was no reason to connect these observations and none of them made sense. Investigation of the specificity of the IgE present in the sera of patients before their first cetuximab treatment necessitated the development of an assay for IgE to cetuximab. This assay was simplified because a technique in which the target antigen was biotinylated and then bound to streptavidin ImmunoCAP (Phadia, Portage, MI) had been established in the previous year.[10] At that point, we were