

Clinical Communications

First-dose anaphylaxis to infliximab: a case of mammalian meat allergy

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Clinical Implications

- IgE antibodies to galactose- α -1,3-galactose, identified in patients with mammalian meat allergy, can cross-react with a glycosylated component of infliximab, resulting in anaphylaxis in patients who receive this therapy.
- In patients with mammalian meat allergy, nonglycosylated monoclonal antibodies should be considered for therapy.

TO THE EDITOR:

We present a case of first-dose anaphylaxis to infliximab in a 53-year-old woman with Crohn's disease. The patient was found to have IgE antibodies to galactose- α -1,3-galactose, which were identified as the cause of the patient's allergic reaction to both infliximab and mammalian meat. This reaction has been previously described with cetuximab, but has not been described with infliximab. Mammalian meat allergy (MMA) is an evolving entity in the United States, Europe, and Australia, and caution should be taken in a patient with MMA before use of infliximab.

Infliximab is a monoclonal antibody (mAb) directed at tumor necrosis factor alpha, a key cytokine that contributes to inflammation in Crohn's disease and ulcerative colitis. Infliximab can provide significant benefit in patients with inflammatory bowel disease, but has been associated with the development of immediate infusion-related adverse events in 5% to 23% of patients.¹ Infusion reactions generally occur after repeated drug exposure; reactions rarely develop during an initial infusion of infliximab.²

Mammalian meat allergy (MMA) is an IgE antibody-mediated response to a mammalian oligosaccharide epitope, galactose- α -1,3-galactose (alpha-gal), found in the major blood groups of nonprimate mammals. Anaphylaxis may occur after patients bitten by a lone star tick, *Amblyomma americanum*, develop IgE antibodies to alpha-gal and ingest mammalian products such as beef, pork, or lamb.³ This typically results in a delayed-onset reaction, with episodes of urticaria, angioedema, and recurrent anaphylaxis often in combination with gastrointestinal symptoms. The exact mechanism by which ticks induce this response is unknown, but hypotheses include the following: (1) IgE antibody expression is induced by the normal saliva of ticks; (2) mammalian glycoproteins or glycolipids from a prior blood meal are present in the tick and trigger development of IgE antibodies targeting alpha-gal; and (3) another organism within the tick is responsible for the IgE development.³

Specific IgE directed against alpha-gal was identified as the cause of immediate anaphylactic reactions during clinical trials evaluating the mAb cetuximab, an agent targeting epidermal growth factor receptor. Cetuximab is glycosylated with alpha-gal

in the mouse-derived SP2/0 cell line, and can result in severe IgE-mediated hypersensitivity reactions in susceptible individuals, some fatal.⁴ Abciximab, basiliximab, canakinumab, infliximab, golimumab, and ustekinumab are all mAbs derived using this same cell line.^{5,6} On the basis of its shared derivation with cetuximab, we hypothesized that infliximab would carry a risk of IgE-mediated anaphylaxis in patients with MMA.

A 53-year-old woman with a history of Crohn's disease was initiated on infliximab. Her history was notable for MMA, which had been confirmed via intradermal testing with positive reactions to beef, lamb, and pork but negative reactions to chicken, turkey, milk, and fish. Serologic testing in this patient confirmed elevated IgE antibodies against alpha-gal at 7.59 IU/mL (reference <0.35 IU/mL).

With her first infliximab infusion, she developed diffuse urticaria and pruritus indicative of a pre-existing IgE response. She was pretreated with prednisone and diphenhydramine before her second infusion, but developed an identical reaction that resulted in the discontinuation of the infusion. She was subsequently started on vedolizumab without adverse effect.

Serum samples from this patient, in addition to serum from 3 patients with known MMA and 2 controls, were analyzed. A comparison was made between mAbs that contain glycosylation with alpha-gal (cetuximab, infliximab, and natalizumab) and those that do not (rituximab and vedolizumab). Total and specific IgE antibodies were measured by ImmunoCAP (Phadia AB, Uppsala, Sweden) or the modified assay with a streptavidin-coated solid phase.⁴ Each monoclonal antibody was biotinylated as described with 5 μ g added to the solid phase. The assays were performed with the ImmunoCAP250 instrument, with a threshold value for a positive reaction of 0.35 IU/mL.

As shown in Table 1, positive responses to mAbs containing alpha-gal moieties were seen in our patient and all 3 individuals with known MMA, but not in nonallergic controls. No reaction was seen to the nonglycosylated mAbs, rituximab or vedolizumab, in either the MMA or nonallergic subjects.

We describe an IgE-mediated hypersensitivity reaction to infliximab in a patient with MMA. The potential for IgE-mediated reactions to mAbs has been reported with first-dose anaphylactic reactions to cetuximab.⁷ Researchers identified IgE antibodies directed against alpha-gal glycosylation of cetuximab as the cause of hypersensitivity and subsequent work identified this as the cause of MMA.⁸

To our knowledge, this is the first reported case of an allergic reaction to infliximab caused by IgE-mediated hypersensitivity to alpha-gal. All 3 mAbs with a positive response (cetuximab, infliximab, and natalizumab) are known to be manufactured in cell lines that glycosylate with alpha-gal. The basis for the cross-reactivity with IgE antibodies directed toward alpha-gal is thought to be their shared production in the murine myeloma cell line SP2/0.⁵ Vedolizumab, a gut-selective humanized IgG1 mAb directed against the α 4 β 7 integrin, is produced in Chinese hamster ovary (CHO) cells, as are rituximab,⁶ mepolizumab,⁹ and omalizumab.⁶ CHO cells have demonstrated the ability to produce alpha-gal in some antibodies, but glycosylation is rare and often at undetectable levels, thus providing a basis for the lack of reported anaphylaxis.⁵ Other mAbs such as reslizumab

TABLE I. Specific IgE levels in serum samples of controls and patients with mammalian meat allergy in response to various monoclonal antibodies (IU/mL)

Subject	Cetuximab	Infliximab	Natalizumab	Rituximab	Vedolizumab	Total IgE
Affected subject	8.06	1.16	1.25	<0.35	<0.35	58.5
Alpha-gal#1	18.4	<0.35	<0.35	<0.35	<0.35	286
Alpha-gal#2	49.5	4.35	2.52	<0.35	<0.35	409
Alpha-gal#3	63.2	10.6	10.6	<0.35	<0.35	1315
Control#1	<0.35	<0.35	<0.35	<0.35	<0.35	<2.00
Control#2	<0.35	<0.35	<0.35	<0.35	<0.35	6.50

Threshold value for a positive reaction was 0.35 IU/mL and all positive values are denoted by bold font. Alpha-gal, patients with allergy to galactose- α -1,3-galactose.

and natalizumab are produced in NS0, another murine myeloma cell line, and can contain alpha-gal moieties that could cause anaphylaxis by cross-reacting with alpha-gal.

Interestingly, 1 patient (alpha-gal #1) demonstrated a positive reaction with cetuximab but not with infliximab or natalizumab, consistent with the previous literature.⁵ This may represent a limitation in our assay, which was able to detect positive reactions to both infliximab and natalizumab in our affected patient and 2 subjects with MMA, consistent with our hypothesis. It remains unclear whether nonspecific binding of IgE to infliximab and natalizumab may have also played a role in our positive results, as patients alpha-gal #2 and #3 had high total IgE levels.

van Bueren et al⁵ showed that intact infliximab has not previously bound specific IgE in experiments using serum from patients with alpha-gal for several reasons. First, the location of alpha-gal on infliximab is the Fc domain (as opposed to the Fc and Fab domains of cetuximab), providing shielding from cross-linking with IgE molecules. Second, the relative avidity of IgE molecules for mono-alpha-galactosylated glycans present in the Fc domains is less than that for the bi-alpha-galactosylated biantennary complex glycans, found on the Fab domains of molecules such as cetuximab (but not infliximab). Lastly, the alpha-gal content of cetuximab is approximately 4.6 times that of infliximab.⁵ As a result, anaphylaxis to infliximab in patients with MMA is exceedingly rare in comparison with anaphylaxis to cetuximab, and our case represents a unique phenomenon.

Based on these data, caution should be taken in any patient with known MMA before the use of infliximab, and alternative agents considered.

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