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Anaphylaxis after Zoster Vaccine: Implicating Alpha-Gal Allergy as a Possible Mechanism

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Capsule Summary

A patient with alpha-gal allergy presented with anaphylaxis after receiving zoster vaccine. Subsequent testing of selected vaccines revealed the presence of alpha-gal allergen in MMR and zoster vaccines, which have in common a higher content of gelatin and content of bovine calf serum.

Keywords

galactose-alpha-1; 3-galactose; alpha-gal; anaphylaxis; vaccine; zoster; gelatin; MMR

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To the Editor

In the Southeastern United States, galactose-alpha-1,3-galactose (alpha-gal) sensitivity has emerged as an etiology of red meat allergy that is causally linked to bites from the lone star tick.[1] Alpha-gal sensitivity often presents with delayed anaphylaxis after consumption of red meat, with lesser degrees of reactivity to milk and gelatin. Gelatin and other non-primate mammalian derived products are common excipient ingredients in several vaccines,[2, 3] and it has been postulated that alpha-gal allergic patients might react to these vaccines.[4]

A patient in our clinic with a documented history of red meat allergy since November 2008 required emergency department treatment and epinephrine administration upon receipt of live attenuated herpes zoster vaccine containing the Oka VZV strain in September 2014. Within minutes of vaccine administration in a local pharmacy she had a sensation of mental clouding progressing to lightheadedness, wheezing, and throat tightness and she self-administered 50 mg diphenhydramine five minutes after symptom onset. She sought emergency care 30 minutes after vaccine receipt at which point she was documented to be dyspneic, flushed, with facial, oral and uvular angioedema and bilateral conjunctival injections with stable vital signs and blood pressure of 149/83, without documented wheezing on pulmonary examination. She was placed on oxygen and administered an additional 25mg of diphenhydramine, 8mg of intramuscular dexamethasone, 20mg of famotidine, nebulized albuterol and 0.3mg of intramuscular epinephrine for her respiratory distress, angioedema, and cutaneous signs.[5] Her symptoms resolved within 20–30 minutes and she was discharged uneventfully after 3 hours observation.

She originally presented to our clinic in 2009 at age 63 with a history of recurrent delayed anaphylaxis, occurring 4–6 hours after eating, and was evaluated for food allergies. At that time, laboratory evaluation in our clinic showed elevated blood specific IgE (sIgE) to beef = 10.5 kU/L, pork = 10.4kU/L, and cow's milk = 2.90kU/L (reference for all <0.35 kU/L). Other food IgEs were within normal limits, as was serum tryptase. She reported that eating any and all mammalian meat would trigger her symptoms. She also reported delayed abdominal symptoms, malaise, and diarrhea with consumption of dairy products. She lived in a rural area, and frequently found lone star ticks embedded in her skin.

One month after her episode of anaphylaxis following vaccination in 2014, she was tested for alpha- gal allergy, with galactose-alpha-1,3-galactose sIgE = 32.5 kU/L, beef sIgE = 23.1 kU/L, lamb/mutton sIgE = 12.2kU/L, and pork sIgE = 17.1 kU/L. She was subsequently tested in 2015 for allergy to gelatin, with porcine gelatin sIgE = 1.84kU/L, and bovine gelatin sIgE = 0.15kU/L (reference range for all sIgE tests <0.35kU/L).

We reviewed publicly available data from a searchable version of the Vaccine Adverse Event Reporting System (VAERS) database[6] using search terms of severe adverse events occurring on the same day of vaccine administration of the Oka VZV strain. Out of 202 reported events, we encountered 14 cases of adverse reaction to zoster vaccine consistent with anaphylaxis. 5/14 (36%) of these potential cases of anaphylaxis had a known associated beef, pork, gelatin, or alpha-gal allergy, and 4 of those 5 cases were reported as taking place in the Southeast United States (Online Table).

We next proceeded to identification of five candidate vaccines that might contain alpha-gal antigen due to content of bovine or porcine derived products.[2, 3] (Table I)

We then evaluated if sera from alpha-gal allergic patients would interact with components of the candidate vaccines. To evaluate, we performed a direct biotinylation of each of the vaccines in full prescribed dose, after which protein concentration was determined and 5μg of biotinylated antigen was added to each streptavidin ImmunoCAP, in two identical trials. Forty microliters of undiluted serum from our index patient along with serum from three additional subjects with alpha-gal allergy was used in each sIgE assay to assess for IgE binding to the vaccines or gelatin (commercially available ImmunoCAP assay c74), similar to previously published methods.[1,7] Serum from the same subjects was also pre-incubated with 50μL of bovine thyroglobulin (BT), a source of alpha-gal antigen, coupled to sepharose bead slurry to deplete alpha-gal sIgE. Assays for binding to biotinylated vaccines were then repeated in two trials to determine whether binding decreased following pre-incubation with bovine thyroglobulin, which suggests that any observed binding to vaccines was actually for alpha-gal. This was performed using previously published methods[1].

The largest direct binding response that could be removed by the presence of bovine thyroglobulin was seen in the index patient to MMR and zoster vaccine (0.96–1.31 IU/ml, Table IIA). There was also low positive binding (values were 0.27 – 0.45IU/ml) for MMR and zoster vaccine in sera from the subjects A and B that could be removed by the presence of bovine thyroglobulin, though sera from subject C did not demonstrate binding to any of the candidate vaccines. The direct binding “vaccine caps” method suggests the presence of an epitope in MMR and zoster vaccine that is recognized by alpha-gal IgE in sera from both the index patient and alpha-gal allergic subjects A & B. (Table IIA)

We next measured the baseline alpha-gal IgE titers in sera from our index patient and the same three additional subjects. To ascertain the presence of vaccine epitopes that would bind/remove alpha-gal specific IgE in excess of that expected for gelatin alone, we incubated sera samples from the index patient and the three alpha-gal positive subjects overnight, separately, with 100μg from each of the five vaccines, bovine gelatin, and porcine gelatin and re-measured alpha-gal IgE titers. (Table IIB).

Incubation of the sera samples overnight showed partial depletion of the alpha-gal IgE response in sera from all four subjects when it was pre-incubated with zoster vaccine and MMR, greater than that for gelatin alone. There were also partial depletions observed in response to the yellow fever vaccine in subjects B and C. While we did note some expected variability in epitope binding to alpha-gal IgE, both MMR and zoster vaccines consistently removed a portion of alpha-gal sIgE response upon re-assay. We did not observe any evidence of epitope binding to alpha-gal IgE binding with either version of TDaP vaccine.

To our knowledge, this is the first report of vaccine induced anaphylaxis associated with alpha-gal allergy. We are somewhat limited in our claim of complete causality by the presence of low level IgE antibodies to porcine gelatin in our patient. Nevertheless, the presence of antigen binding directly to alpha-gal IgE found in patient sera and depletion of alpha-gal sIgE in overnight incubation with both MMR and zoster vaccine would suggest

that either their increased gelatin content or some other shared element in the manufacturing process of these two vaccines increases the likelihood of alpha-gal contamination. Both MMR and zoster vaccine use bovine calf serum during their production, and hypothetically additional alpha-gal antigen could be acquired at this step. The lesser reactivity to yellow fever vaccine (which has a lower gelatin content), and absent reactivity to two different TDaP vaccines, which contain other bovine derived products but not gelatin, is also helpful, as patients with this allergy would be unlikely to react to these vaccines. There are other vaccines that contain mammalian products, but our findings would suggest that alpha-gal content is highest in MMR and zoster vaccine.

Alpha-gal allergy is an increasingly prevalent hypersensitivity syndrome in the Southeast US, as well as other parts of the world. Clinicians who manage it should be made aware of a risk of anaphylaxis to higher content gelatin containing vaccines such as MMR and zoster vaccine, especially because of their parenteral delivery. While anaphylaxis from zoster vaccine appears to be a low probability event,[8] it has significant public health implications, and there is a need to determine on a population level how often patients who have anaphylaxis to higher gelatin content vaccines such as MMR and Zoster vaccine have an underlying alpha-gal allergy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I

Reported Gelatin or Mammal Derived Product Content of Selected Vaccines

Vaccine	Reported Gelatin Content of Vaccine	Reported Type of Gelatin or Animal Derived Product
Zoster (*Merck)*	15,580 μg per 0.65 mL dose	Porcine Gelatin, Bovine Calf Serum
Measles, Mumps and Rubella (MMR) (*Merck*)	14,500 μg per 0.5 mL dose	Bovine Gelatin, Bovine Calf Serum
Yellow Fever (*Sanofi Pasteur*)	7,500 μg per 0.5 mL dose	Gelatin, type not reported
Tetanus, Diptheria and acellular Pertussis (TDaP) (*GSK*)	None	Bovine Casein, Bovine Extract
Tetanus, Diptheria and acellular Pertussis (TDaP) (*Sanofi Pasteur*)	None	Bovine Casamino Acids

Table II

Serologic Assays for Alpha-gal in Selected Vaccines

A: IgE binding (kU/ml) to biotinylated vaccines assayed with alpha-gal positive sera from three subjects, with and without bovine thyroglobulin (BT) to deplete alpha gal IgE											
	TDaP (Sanofi)		TDaP (GSK)		MMR		Yellow Fever		Zoster		Gelatin Immunocap c74
	Trial 1	*Trial 2*	*Trial 1*	*Trial 2*	*Trial 1*	*Trial 2*	*Trial 1*	*Trial 2*	*Trial 1*	*Trial 2*	*Baseline*
Index Patient	<0.1	0.11	<0.1	<0.1	1.31	1.22	0.27	0.25	1.14	0.96	0.16
w/BT Beads	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.13	<0.1	<0.1	
Subject A	0.10	0.11	0.11	<0.1	0.27	0.28	0.41	0.37	0.34	0.35	<0.1
w/BT Beads	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.39	0.40	<0.1	<0.1	
Subject B	1.28	1.43	1.06	1.63	1.46	1.16	0.90	1.18	1.04	1.16	0.72
w/BT Beads	1.06	1.30	1.22	1.20	1.05	0.91	0.90	1.12	0.60	0.76	
Subject C	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
w/BT Beads	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	

B: Serum alpha-gal IgE (kU/ml) levels at baseline and after overnight incubation with vaccines and gelatins								
	Baseline	TDaP (Sanofi)	TDaP (GSK)	MMR	Yellow Fever	Zoster	Porcine Gelatin	Bovine Gelatin
Index Patient	58.3	55.9	57.8	31.2	56.9	33.1	54.7	56.6
Subject A	>100	>100	>100	0.96	>100	91.4	>100	>100
Subject B	>100	>100	>100	71.5	87.6	83.3	94.6	97.3
Subject C	84.4	72.6	86.9	60.7	75.7	56	82.8	81

BT= Bovine Thyroglobulin. All values are in units of kU/mL.

All values in units of kU/mL). Baseline values are the patient's serum alpha-gal IgE values prior to overnight incubation.