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

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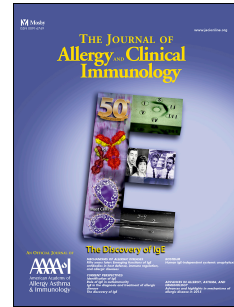
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1 Anaphylaxis after Zoster Vaccine: Implicating Alpha-Gal Allergy as a Possible
2 Mechanism

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46 University of Virginia, and the University of North Carolina.

47

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

52

53 Key Words: galactose-alpha-1, 3-galactose, alpha-gal, anaphylaxis, vaccine, zoster,
54 gelatin, MMR

55

56

57 To the Editor: In the Southeastern United States, galactose-alpha-1,3-galactose (alpha-

58 gal) sensitivity has emerged as an etiology of red meat allergy that is causally linked to

59 bites from the lone star tick.¹ Alpha-gal sensitivity often presents with delayed

60 anaphylaxis after consumption of red meat, with lesser degrees of reactivity to milk and

61 gelatin. Gelatin and other non-primate mammalian derived products are common

62 excipient ingredients in several vaccines,^{2,3} and it has been postulated that alpha-gal

63 allergic patients might react to these vaccines.⁴

64

65 A patient in our clinic with a documented history of red meat allergy since November

66 2008 required emergency department treatment and epinephrine administration upon

67 receipt of live attenuated herpes zoster vaccine containing the Oka VZV strain in

68 September 2014. Within minutes of vaccine administration in a local pharmacy she had a

69 sensation of mental clouding progressing to lightheadedness, wheezing, and throat

70 tightness and she self-administered 50 mg diphenhydramine five minutes after symptom

71 onset. She sought emergency care 30 minutes after vaccine receipt at which point she was

72 documented to be dyspneic, flushed, with facial, oral and uvular angioedema and bilateral

73 conjunctival injections with stable vital signs and blood pressure of 149/83, without

74 documented wheezing on pulmonary examination. She was placed on oxygen and

75 administered an additional 25mg of diphenhydramine, 8mg of intramuscular
76 dexamethasone, 20mg of famotidine, nebulized albuterol and 0.3mg of intramuscular
77 epinephrine for her respiratory distress, angioedema, and cutaneous signs.⁵ Her
78 symptoms resolved within 20-30 minutes and she was discharged uneventfully after 3
79 hours observation.

80

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

89

90 One month after her episode of anaphylaxis following vaccination in 2014, she was tested
91 for alpha- gal allergy, with galactose-alpha-1,3-galactose sIgE = 32.5 kU/L, beef sIgE =
92 23.1 kU/L, lamb/mutton sIgE = 12.2kU/L, and pork sIgE = 17.1 kU/L. She was
93 subsequently tested in 2015 for allergy to gelatin, with porcine gelatin sIgE = 1.84kU/L,
94 and bovine gelatin sIgE = 0.15kU/L (reference range for all sIgE tests <0.35kU/L).

95

96 We reviewed publicly available data from a searchable version of the Vaccine Adverse
97 Event Reporting System (VAERS) database⁶ using search terms of severe adverse events

98 occurring on the same day of vaccine administration of the Oka VZV strain. Out of 202
99 reported events, we encountered 14 cases of adverse reaction to zoster vaccine consistent
100 with anaphylaxis. 5/14 (36%) of these potential cases of anaphylaxis had a known
101 associated beef, pork, gelatin, or alpha-gal allergy, and 4 of those 5 cases were reported
102 as taking place in the Southeast United States (**Online Table**).

103

104 We next proceeded to identification of five candidate vaccines that might contain alpha-
105 gal antigen due to content of bovine or porcine derived products.^{2,3} (**Table I**)

106

107 We then evaluated if sera from alpha-gal allergic patients would interact with
108 components of the candidate vaccines. To evaluate, we performed a direct biotinylation
109 of each of the vaccines in full prescribed dose, after which protein concentration was
110 determined and 5µg of biotinylated antigen was added to each streptavidin ImmunoCAP,
111 in two identical trials. Forty microliters of undiluted serum from our index patient along
112 with serum from three additional subjects with alpha-gal allergy was used in each sIgE
113 assay to assess for IgE binding to the vaccines or gelatin (commercially available
114 ImmunoCAP assay c74), similar to previously published methods.^{1,7} Serum from the
115 same subjects was also pre-incubated with 50µL of bovine thyroglobulin (BT), a source
116 of alpha-gal antigen, coupled to sepharose bead slurry to deplete alpha-gal sIgE. Assays
117 for binding to biotinylated vaccines were then repeated in two trials to determine whether
118 binding decreased following pre-incubation with bovine thyroglobulin, which suggests
119 that any observed binding to vaccines was actually for alpha-gal. This was performed
120 using previously published methods¹.

121

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

131

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

138

139 Incubation of the sera samples overnight showed partial depletion of the alpha-gal IgE
140 response in sera from all four subjects when it was pre-incubated with zoster vaccine and
141 MMR, greater than that for gelatin alone. There were also partial depletions observed in
142 response to the yellow fever vaccine in subjects B and C. While we did note some
143 expected variability in epitope binding to alpha-gal IgE, both MMR and zoster vaccines

144 consistently removed a portion of alpha-gal sIgE response upon re-assay. We did not
145 observe any evidence of epitope binding to alpha-gal IgE binding with either version of
146 TDaP vaccine.

147

148 To our knowledge, this is the first report of vaccine induced anaphylaxis associated with
149 alpha-gal allergy. We are somewhat limited in our claim of complete causality by the
150 presence of low level IgE antibodies to porcine gelatin in our patient. Nevertheless, the
151 presence of antigen binding directly to alpha-gal IgE found in patient sera and depletion
152 of alpha-gal sIgE in overnight incubation with both MMR and zoster vaccine would
153 suggest that either their increased gelatin content or some other shared element in the
154 manufacturing process of these two vaccines increases the likelihood of alpha-gal
155 contamination. Both MMR and zoster vaccine use bovine calf serum during their
156 production, and hypothetically additional alpha-gal antigen could be acquired at this step.
157 The lesser reactivity to yellow fever vaccine (which has a lower gelatin content), and
158 absent reactivity to two different TDaP vaccines, which contain other bovine derived
159 products but not gelatin, is also helpful, as patients with this allergy would be unlikely to
160 react to these vaccines. There are other vaccines that contain mammalian products, but
161 our findings would suggest that alpha-gal content is highest in MMR and zoster vaccine.

162

163 Alpha-gal allergy is an increasingly prevalent hypersensitivity syndrome in the Southeast
164 US, as well as other parts of the world. Clinicians who manage it should be made aware
165 of a risk of anaphylaxis to higher content gelatin containing vaccines such as MMR and
166 zoster vaccine, especially because of their parenteral delivery. While anaphylaxis from

167 zoster vaccine appears to be a low probability event,⁸ it has significant public health
168 implications, and there is a need to determine on a population level how often patients
169 who have anaphylaxis to higher gelatin content vaccines such as MMR and Zoster
170 vaccine have an underlying alpha-gal allergy.

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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 (<i>Merck</i>)	15,580 µg per 0.65 mL dose	Porcine Gelatin, Bovine Calf Serum
Measles, Mumps and Rubella (MMR) (<i>Merck</i>)	14,500 µg per 0.5 mL dose	Bovine Gelatin, Bovine Calf Serum
Yellow Fever (<i>Sanofi Pasteur</i>)	7,500 µg per 0.5 mL dose	Gelatin, type not reported
Tetanus, Diphtheria and acellular Pertussis (TDaP) (<i>GSK</i>)	None	Bovine Casein, Bovine Extract
Tetanus, Diphtheria and acellular Pertussis (TDaP) (<i>Sanofi Pasteur</i>)	None	Bovine Casamino Acids

227

228

229

Table II: Serologic Assays for Alpha-gal in Selected Vaccines

IIA: 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 <i>Baseline</i>
	<i>Trial 1</i>	<i>Trial 2</i>	<i>Trial 1</i>	<i>Trial 2</i>	<i>Trial 1</i>	<i>Trial 2</i>	<i>Trial 1</i>	<i>Trial 2</i>	<i>Trial 1</i>	<i>Trial 2</i>	
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	

230

IIB: 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

231

232 **Table IIA: BT= Bovine Thyroglobulin. All values are in units of kU/mL.**233 **Table IIB: All values in units of kU/mL). Baseline values are the patient's serum alpha-gal IgE**234 **values prior to overnight incubation.**

235

236

Online Supplement Table I: Reported cases* of anaphylaxis associated with the live attenuated Oka strain zoster vaccine in patients with coexisting beef, pork, gelatin, or alpha-gal allergy			
Case (Year)	Reaction	Associated Allergy	Location
76 Year Old Female (2007)	20 minutes after vaccine receipt at a pharmacy developed anaphylaxis, admitted for overnight hospital stay. Description of the event is limited. Diagnosed as anaphylaxis by treating physician.	Positive specific IgE to Beef, pork, bovine gelatin, porcine gelatin, titers not reported. Reported negative alpha gal sIgE.	Maryland
70 Year Old Female (2008)	Developed life threatening hypotension, shortness of breath, angioedema shortly after vaccine receipt, with overnight hospital stay, treatment not reported. Diagnosed as anaphylaxis by treating physician.	Clinical report of preexisting beef, pork, dairy allergy. sIgE testing and titers not reported. Alpha-gal status and sIgE testing not reported	Arkansas
70 Year Old Female (2009)	Patient developed immediate severe allergic reaction upon receipt of vaccine in a pharmacy. Was taken to the emergency room, received epinephrine for treatment of hypotension. Diagnosed as anaphylaxis by treating physician.	Report of positive testing to gelatin, not reported if testing was skin or sIgE testing. Beef, pork, alpha-gal allergy status, sIgE testing and titers not reported.	Location not reported
61 Year Old Male (2013)	Patient developed disseminated rash shortly after vaccine receipt at a pharmacy. Returned to pharmacy and was given diphenhydramine 25mg. After 10 minutes of observation, patient developed dizziness and syncope. IM epinephrine was administered, and patient was transferred by EMS to hospital. Vital signs not reported.	Clinical report of preexisting beef and pork allergy. Results of sIgE testing and titers not reported.	Virginia
63 Year Old	5 minutes after vaccine receipt, patient developed generalized	Beef, pork, alpha-gal allergy reported.	Maryland

Male (2015)	itching followed by generalized hives and throat discomfort, resolution with diphenhydramine in the emergency department. Diagnosed as anaphylaxis by treating physician.	Reported sIgE porcine gelatin=0.58 kU/L, bovine gelatin <0.10kU/L, alpha-gal=3.70 kU/L	
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***Case Definition:**

1) a provider diagnosis of anaphylaxis or 2) use of published criteria for defining cases of vaccine-associated anaphylaxis when provider diagnosis was not reported.¹

Supplemental References:

A previous report indicates an increased likelihood of gelatin hypersensitivity when alpha-gal allergy is present.² Parenteral route of administration was also reported to increase the likelihood of allergic response, and alpha-gal was detected in gelatin colloids.² In studies of Japanese Encephalitis Virus Vaccine, reductions in gelatin content reduced the likelihood of anaphylaxis.³ In reviewing the original randomized controlled trial of zoster vaccine, there was one episode of an anaphylactic event in a patient who received the gelatin placebo.⁴

An important question is whether there is a reactivity threshold that can be tested to predetermine the likelihood of anaphylaxis to zoster vaccine in patients with alpha-gal allergy. Our patient had high titer alpha-gal IgE antibody and anaphylaxis. In contrast, administration of zoster vaccine without any adverse reaction has been reported in an alpha-gal allergic patient with a lower titer of alpha-gal IgE (alpha-gal sIgE = 6.0 kU/L).⁵

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