Session 4008: Diagnosing an Allergy to Galactose-alpha-1,3-Galactose

AAAAAI Annual Meeting

Seminar
March 3, 2014
High incidence of hypersensitivity reactions to cetuximab infusions in mid-Missouri: Association with prior history of atopy

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Measurement of IgE ab to Purified Allergens Using Streptavidin Solid Phase

“Allergen” of interest (cetuximab) + Biotin

Streptavidin Solid Phase + Biotinylated “Allergen”

Solid Phase*

Then add serum; wash; add labeled anti-IgE; detect chemilum.

*Routine assay technique in parallel with Phadia standard curve gives results in IU/ml.
IgE Antibodies Binding to Cetuximab in Sera from 76 Case Subjects and 462 Controls
Cetuximab

Typical Fc region oligos:
- core fucosylated biantennary oligos;
- no alpha-gal or NGNA

Glycosylation Site Including
α-gal and Sialic Acid

Murine [Blue]

F(ab′)_2

N-43 *

N-88

Pepsin Digestion

Fc

Typical Fc region oligos:
- core fucosylated biantennary oligos;
- no alpha-gal or NGNA

Glycosylation Site Including
only carbohydrates common in humans

Human [White]

Site not glycosylated
What is alpha-gal?

- Carbohydrate synthesized by the glycosylation enzyme alpha-1,3-galactosyltransferase
- Alpha-gal epitope is present on the tissues and cells of all lower mammals
- Humans and apes, however, do not have alpha-gal due to an inactive gene product
II. DEFINING A “NEW” FOOD ALLERGY
Table 3. Specificity of the IgE Antibodies That Cross-React with Cetuximab.*

<table>
<thead>
<tr>
<th>Type of Reaction and Subject No.</th>
<th>Type of Cetuximab</th>
<th>Galactose-α-1,3-Galactose</th>
<th>Mammalian Allergens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SP2/0</td>
<td>CHO</td>
<td>Mouse IgG</td>
</tr>
<tr>
<td>Hypersensitivity reaction</td>
<td></td>
<td></td>
<td>international units per milliliter</td>
</tr>
<tr>
<td>Anaphylaxis related to cetuximab</td>
<td></td>
<td></td>
<td>0.35</td>
</tr>
<tr>
<td>1</td>
<td>41.6</td>
<td>0.35</td>
<td>13.8</td>
</tr>
<tr>
<td>2</td>
<td>38.8</td>
<td>0.35</td>
<td>35.2</td>
</tr>
<tr>
<td>3</td>
<td>20.2</td>
<td>0.35</td>
<td>12.6</td>
</tr>
<tr>
<td>4</td>
<td>11.1</td>
<td>0.35</td>
<td>2.9</td>
</tr>
<tr>
<td>5</td>
<td>4.9</td>
<td>0.35</td>
<td>2.0</td>
</tr>
<tr>
<td>6</td>
<td>4.2</td>
<td>0.35</td>
<td>2.7</td>
</tr>
<tr>
<td>Recurrent anaphylaxis unrelated to cetuximab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>131.0</td>
<td>1.89</td>
<td>38.9</td>
</tr>
<tr>
<td>8</td>
<td>69.2</td>
<td>0.35</td>
<td>42.1</td>
</tr>
<tr>
<td>9</td>
<td>55.1</td>
<td>0.35</td>
<td>32.2</td>
</tr>
<tr>
<td>10</td>
<td>43.5</td>
<td>0.35</td>
<td>32.3</td>
</tr>
<tr>
<td>11</td>
<td>81.1</td>
<td>0.35</td>
<td>100.0</td>
</tr>
<tr>
<td>12</td>
<td>13.0</td>
<td>0.35</td>
<td>9.0</td>
</tr>
<tr>
<td>Mean</td>
<td>27.7</td>
<td>NA</td>
<td>25.5</td>
</tr>
<tr>
<td>No hypersensitivity reaction</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Chung CH et al. N Engl J Med 2008;358:1109-1117
Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose-\(\alpha-1,3\)-galactose

Scott P. Commins, MD, PhD,\textsuperscript{a} Shama M. Satinover, MS,\textsuperscript{a} Jacob Hosen, BS,\textsuperscript{a} Jonathan Mozena, MD,\textsuperscript{b} Larry Borish, MD,\textsuperscript{a} Barrett D. Lewis, MD,\textsuperscript{c} Judith A. Woodfolk, MBChB, PhD,\textsuperscript{a} and Thomas A. E. Platts-Mills, MD, PhD\textsuperscript{a} Charlottesville and Fredericksburg, Va, and Springfield, Mo

- 24 patients
- Virginia & Missouri
- Symptoms delayed 3-6 hours after eating mammalian meat
- Prick skin test often less than 4mm
- Intradermal skin test positive
Skin Testing Results: Often <4mm SPT

Prick test performed using lancette and intradermal testing with 25 gauge needle in the same patient on a single clinic visit.

Commins et al JACI 2009
CAP-RAST of Specific IgE Abs in Patients with anti-Gal IgE

Foods

- Alpha-Gal
- Beef
- Pork
- Lamb
- Chicken
- Turkey
- Fish

Inhalants

- Cat
- Fel d 1
- Dog
- Dust Mite
- Timothy Grass

Specific IgE Abs (IU/mL)

- Limit of detection

- $r = 0.81$
- $r = 0.98$

Symbols:

- ▼ x1
- ♦ x1
- ● x3
- □ x12
- △ x11
- ▽ x12
- □ x1
- ○ x7
- ● x1
- □ x9
- ♦ x4
Cat epithelium contains protein allergens AND alpha-gal

protein x attached to α-gal

Fel d 1

Gal
Gal
GlcNAc
Galα(1,3)Gal

α-gal
Alpha-gal specific IgE is associated with anaphylaxis but not asthma

(Figure adapted from Commins, Kelly...Platts-Mills, AJRCCM, 2012)

Alpha-gal specific IgE (IU/mL)

Limit of detection

Reactions include anaphylaxis

Cat in home
(N = 96)

No cat in home
(N = 112)

Asthma
(N = 68)

Clinic controls
(N = 59)

Anaphylaxis/urticaria subjects

Number <0.35

< 0.1

0.1

0.35

x 8

x 13

x 58

x 55

0.35

1

10

100

1000
Alpha-gal specific IgE vs Total IgE in Patients with Red Meat Allergy

$r = 0.60, p<0.001$

(Commins, Kelly...Platts-Mills, AJRCCM, 2012)
<table>
<thead>
<tr>
<th><strong>IgE Ab to alpha-gal in kids (n=45)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (% male)</td>
</tr>
<tr>
<td>Mean age at presentation (Range)</td>
</tr>
<tr>
<td>Geometric Mean of Total IgE (95% CI)</td>
</tr>
<tr>
<td><strong>Symptoms at presentation</strong></td>
</tr>
<tr>
<td>Anaphylaxis*</td>
</tr>
<tr>
<td>Gastrointestinal/ Oral</td>
</tr>
<tr>
<td>Urticaria</td>
</tr>
<tr>
<td>Angioedema</td>
</tr>
<tr>
<td>Average time to symptoms (Range)</td>
</tr>
<tr>
<td><strong>Tick exposure</strong></td>
</tr>
<tr>
<td>Redness and Itching at site of Tick bite</td>
</tr>
<tr>
<td>Tick borne illness#</td>
</tr>
<tr>
<td><strong>Emergency Department (ED) visits</strong></td>
</tr>
<tr>
<td>Medications administered in ED</td>
</tr>
<tr>
<td>Antihistamines (35%)</td>
</tr>
<tr>
<td>Oral Steroids (19%)</td>
</tr>
<tr>
<td>Parenteral Steroids (17%)</td>
</tr>
<tr>
<td>IV Fluids (17%)</td>
</tr>
<tr>
<td>Hospital Admissions</td>
</tr>
</tbody>
</table>
IgE Ab to alpha-gal in kids (n=45)
Delayed symptoms induced by oral exposure to mammalian proteins in patients with IgE ab to alpha-gal.

• Despite high titer IgE antibodies that bind epitopes on a range of mammalian proteins including beef, pork and lamb:
  – No awareness of immediate response in the mouth (i.e. no lip swelling or tingling).
  – Anaphylaxis occurring after eating beef starts with skin itching 3-6 hours later.
  – Skin prick tests generally <4mm in diameter while intradermals often ≥8mm.
‘Delayed’ food allergy?

• Food allergy symptoms classically occur immediately (OAS), up to 2 hours after eating

• No mention of ‘delayed’ symptoms that can be attributed to food in common allergy texts
Mammalian meat challenge

Subject #FC-10: sIgE to alpha-gal = 29.1 IU/mL; total IgE = 201

4hrs 25min after eating mammalian meat: pruritus followed by urticaria on right flank
Time course of IgE antibodies to alpha-gal and total IgE following episodes of multiple tick bites (red arrows)
Time course of IgE antibodies to alpha-gal and total IgE following episodes of multiple tick bites (red arrows)
Time course of IgE antibodies to alpha-gal and total IgE following episodes of multiple tick bites (red arrows)
IgE to Alpha-gal and Total IgE Rise Following Tick Bites

~50 bites from larval ticks (Sept 4th)
Tracking IgE to Alpha-gal and Total IgE over Time (E202)