We Champion Children by Making Them Better Today and Healthier Tomorrow

DELAYED ANAPHYLAXIS AFTER A TICK BITE:
THE COMPLICATED STORY OF GALACTOSE-ALPHA-1,3-GALACTOSE (ALPHA-GAL)

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Disclosures

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- Consultant: None
Acknowledgements

- Dr. Scott P. Commins, University of North Carolina
Objectives

- Understand the importance of cetuximab in the elucidation of IgE to alpha-1,3-alpha-galactose (alpha-gal).
- Appreciate the clinical symptoms (DELAYED) and laboratory findings of a patient with alpha-gal allergy.
- Identify what alpha-gal allergy looks like in the state of Arkansas.
56 yo man with new onset anaphylaxis

- ED visit
  - Diffuse urticaria that woke him from sleep
  - Immediately took antihistamines
  - Continued progression of hives
  - Abdominal pain and sudden urge to defecate
  - Wife gave him an epi-pen injection and called 911
  - Light-headed and lost consciousness with BP of 74/54 when EMS arrived
  - Received NS bolus in ambulance

In the ED:

- Pressure normalized
- Notable rash with swelling of hands
- No wheezing or audible stridor
- Given steroids, diphenhydramine, and famotidine
- Tryptase was drawn
- Admitted for observation
Laboratory Tests in the Diagnosis of Anaphylaxis

- Plasma histamine
- Serum tryptase
- 24-hr Urinary histamine metabolite

Minutes

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Mast Cell Tryptase in Anaphylaxis

Levels of tryptase in patients with anaphylaxis (n=6), myocardial disease (n=9; 4 with shock), sepsis (n=6, 3 with shock), and systemic mastocystosis (n=17) and in 16 controls.

<table>
<thead>
<tr>
<th>CBC with Differential</th>
<th>Patient Values</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>10.76 k/UL</td>
<td>4.0 –11.0 k/µL</td>
</tr>
<tr>
<td>Neutrophils Percent</td>
<td>53.7 %</td>
<td>47.0 – 82.0 %</td>
</tr>
<tr>
<td>Lymphocytes Percent</td>
<td>34.2 %</td>
<td>15.0 – 45.0 %</td>
</tr>
<tr>
<td>Monocytes Percent</td>
<td>10.1 %</td>
<td>2.0 – 12.0 %</td>
</tr>
<tr>
<td>Eosinophils Percent</td>
<td>1.5 %</td>
<td>0.0 – 6.0 %</td>
</tr>
<tr>
<td>Basophils Percent</td>
<td>0.5 %</td>
<td>0.0 – 2.0 %</td>
</tr>
<tr>
<td>Neutrophils Absolute Count</td>
<td>5.78 k/UL</td>
<td>150 – 450 k/µL</td>
</tr>
<tr>
<td>Lymphocytes Absolute Count</td>
<td>3.68 k/UL</td>
<td>1.00 – 5.00 k/µL</td>
</tr>
<tr>
<td>Monocytes Absolute Count</td>
<td>1.09 k/UL</td>
<td>0.00 – 1.00 k/µL</td>
</tr>
<tr>
<td>Eosinophils Absolute Count</td>
<td>0.16 k/UL</td>
<td>0.00 – 0.60 k/µL</td>
</tr>
<tr>
<td>Basophils Absolute Count</td>
<td>0.05 k/UL</td>
<td>0.00 – 0.20 k/µL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thyroid Studies</th>
<th>Patient Values</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>2.060 µIU/mL</td>
<td>0.47–4.68 µIU/mL</td>
</tr>
<tr>
<td>fT4</td>
<td>1.24 ng/dL</td>
<td>0.65–1.85ng/dL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allergy Evaluation</th>
<th>Patient Values</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tryptase (in ED)</td>
<td>16.3 µg/L</td>
<td>0-11 µg/L</td>
</tr>
<tr>
<td>Tryptase (in clinic)</td>
<td>4 µg/L</td>
<td>0-11 µg/L</td>
</tr>
<tr>
<td>IgE</td>
<td>220 IU/L</td>
<td>2-214 IU/L</td>
</tr>
<tr>
<td>IgE to alpha-gal</td>
<td>45.6 IU/L</td>
<td>&lt;0.35 IU/L</td>
</tr>
</tbody>
</table>

WBC= white blood count; TSH= thyroid stimulating hormone; fT4= free T4; IgE= immunoglobulin E
Further History Revealed

- Similar episode 3 years prior
  - Taken off ACEi
- Occasional urticaria for the next few years
- Started on daily cetirizine for urticaria
  - Urticaria improved, so stopped cetirizine
- Developed more urticaria, which had really “ramped up” in the 2 weeks preceding the anaphylaxis episode
More History

- No new foods, medications, or sting history
- Considerable amount of time outdoors
- Had eaten pork the evening preceding the described presentation

- Kept overnight with resolution of symptoms
- Came to allergy and immunology clinic at UAMS
- Diagnosed with alpha-gal
  - IgE alpha-gal was 45.6 IU/L (nl <0.35)
  - Repeat Tryptase outside the event was 4ug/L
Background

- How oncologists helped uncover a novel food allergy
High incidence of hypersensitivity reactions to cetuximab infusions in mid-Missouri: Association with prior history of atopy

R. Owera, A. Gill, S. Haddadin, R. Khozouz and M. C. Perry
University of Missouri Columbia, Columbia, MO

Cetuximab and Anaphylaxis

Regarding cetuximab HSR:

The story got stranger as O’Neil talked to more oncologists. He heard that a colleague in Nashville, Tennessee, was finding the same problem. But when O’Neil spoke to oncologists from other areas of the country, they didn’t know what he was talking about. A prominent colorectal oncologist in New York “thought we were lying or crazy,” O’Neil recalls.

From “A Mysterious Allergy Afflicts the South” by Sheila Read in Endeavors, 24:2, 2-3, 2008
IgE to Cetuximab Leads to IgE to Alpha-gal: A (very) Brief History


Adapted from Beck et al, *Disc Med* 2010

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**Cetuximab-Induced Anaphylaxis and IgE Specific for Galactose-α-1,3-Galactose**

Christine H. Chung, M.D., Beloo Mirakhur, M.D., Ph.D., Emily Chan, M.D., Ph.D., Quynh-Thu Le, M.D., Jordan Berlin, M.D., Michael Morse, M.D., Barbara A. Murphy, M.D., Shama M. Satinover, M.S., Jacob Hosen, B.S., David Mauro, M.D., Ph.D., Robbert J. Slebos, Ph.D., Qinwei Zhou, Ph.D., Diane Gold, M.D., Tina Hatley, M.D., Daniel J. Hicklin, Ph.D., and Thomas A.E. Platts-Mills, M.D., Ph.D.
What is Alpha-gal?

- Carbohydrate synthesized by the glycosylation enzyme alpha-1,3-galactosyltransferase
- Alpha-gal epitope is present on the tissue and cells of all lower mammals
- Humans and apes, however, do not have alpha-gal due to an inactive gene product
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(\dagger)</th>
<th>Galactose-(\alpha-1,3)-Galactose(\dagger)</th>
<th>Mammalian Allergens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SP2/0(\dagger)</td>
<td>CHO(\dagger)</td>
<td>Mouse IgG(\dagger)</td>
</tr>
<tr>
<td>Hypersensitivity reaction</td>
<td></td>
<td></td>
<td>international units per millilitre</td>
</tr>
<tr>
<td>Anaphylaxis related to cetuximab</td>
<td></td>
<td></td>
<td></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(\dagger)</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>

Defining a “new” Food Allergy

Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose-α-1,3-galactose

Scott P. Commins, MD, PhD, † Shama M. Satinover, MS, ‡ Jacob Hosen, BS, ‡ Jonathan Mozena, MD, ‡ Larry Borish, MD, ‡ Barrett D. Lewis, MD, ‡ Judith A. Woodfolk, MBChB, PhD, § and Thomas A. E. Platts-Mills, MD, PhD ‡ Charlottesville and Fredericksburg, Va, and Springfield, Mo

JACI, February 2009

- 24 patients
- Virginia & Missouri
- Symptoms delayed 3-6 hours after eating mammalian meat
- Prick skin test often less than 4mm
- Intradermal skin test positive
Prick test performed using lancette and intradermal testing with 25 gauge needle in the same patient on a single clinic visit.
# Allergy to Alpha-gal

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age /Sex</th>
<th>Race</th>
<th>Symptoms</th>
<th>Time to Reaction (hours)</th>
<th>Alpha-Gal IgE Titer (IU/mL)</th>
<th>Beef IgE Titer (IU/mL)</th>
<th>Total IgE Titer (IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E001</td>
<td>44 / M</td>
<td>W</td>
<td>ANA</td>
<td>6</td>
<td>67.0</td>
<td>3.48</td>
<td>157</td>
</tr>
<tr>
<td>E008</td>
<td>80 / F</td>
<td>W</td>
<td>AE, U</td>
<td>6</td>
<td>0.52</td>
<td>0.35</td>
<td>45.9</td>
</tr>
<tr>
<td>E018</td>
<td>26 / M</td>
<td>W</td>
<td>ANA</td>
<td>5</td>
<td>59.3</td>
<td>16.6</td>
<td>274</td>
</tr>
<tr>
<td>E022</td>
<td>74 / F</td>
<td>W</td>
<td>AE, U</td>
<td>3</td>
<td>9.03</td>
<td>8.90</td>
<td>66.6</td>
</tr>
<tr>
<td>E026</td>
<td>47 / M</td>
<td>W</td>
<td>ANA</td>
<td>6</td>
<td>&gt;100</td>
<td>32.9</td>
<td>1081</td>
</tr>
<tr>
<td>E030</td>
<td>56 / M</td>
<td>W</td>
<td>U</td>
<td>4-6</td>
<td>80.6</td>
<td>15.8</td>
<td>709</td>
</tr>
<tr>
<td>E031</td>
<td>55 / F</td>
<td>W</td>
<td>U</td>
<td>4</td>
<td>68.9</td>
<td>26.2</td>
<td>243</td>
</tr>
<tr>
<td>E036</td>
<td>66 / M</td>
<td>W</td>
<td>U</td>
<td>4-6</td>
<td>21.1</td>
<td>19.2</td>
<td>262</td>
</tr>
<tr>
<td>E054</td>
<td>45 / M</td>
<td>W</td>
<td>ANA</td>
<td>3</td>
<td>2.42</td>
<td>0.35</td>
<td>244</td>
</tr>
<tr>
<td>E076</td>
<td>50 / M</td>
<td>W</td>
<td>U</td>
<td>4</td>
<td>9.25</td>
<td>3.24</td>
<td>247</td>
</tr>
<tr>
<td>E115</td>
<td>58 / F</td>
<td>W</td>
<td>ANA</td>
<td>2-4</td>
<td>&gt;100</td>
<td>47.8</td>
<td>1622</td>
</tr>
<tr>
<td>E128</td>
<td>37 / M</td>
<td>W</td>
<td>U</td>
<td>4-6</td>
<td>26.8</td>
<td>5.65</td>
<td>886</td>
</tr>
<tr>
<td>E162</td>
<td>39 / F</td>
<td>W</td>
<td>AE, U</td>
<td>6</td>
<td>11.1</td>
<td>1.51</td>
<td>30.5</td>
</tr>
</tbody>
</table>
ImmunoCAP of Specific IgE in Patients with anti-Gal IgE

- **Foods**
  - Alpha-Gal
  - Beef
  - Pork
  - Lamb
  - Chicken
  - Turkey
  - Fish
  - Cat
  - Fel d 1
  - Dog
  - Dust Mite
  - Timothy Grass

- **Inhalants**
  - Specific IgE Abs (IU/mL)

Limit of detection
**IgE antibody to Alpha-gal in Children (n=51)**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (% male)</strong></td>
<td>69%</td>
</tr>
<tr>
<td><strong>Mean age at presentation (Range)</strong></td>
<td>12 (4-17)</td>
</tr>
<tr>
<td><strong>Geometric Mean of Total IgE (95% CI)</strong></td>
<td>147 IU/mL (105-206 IU/mL)</td>
</tr>
<tr>
<td><strong>Symptoms at presentation</strong></td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis*</td>
<td>44%</td>
</tr>
<tr>
<td>Gastrointestinal/Oral</td>
<td>64%</td>
</tr>
<tr>
<td>Urticaria</td>
<td>92%</td>
</tr>
<tr>
<td>Angioedema</td>
<td>31%</td>
</tr>
<tr>
<td><strong>Average time to symptoms (Range)</strong></td>
<td>4.68 hrs (10 mins to 24 hrs)</td>
</tr>
<tr>
<td><strong>Tick exposure</strong></td>
<td>100%</td>
</tr>
<tr>
<td>Redness and Itching at site of Tick bite</td>
<td>87%</td>
</tr>
<tr>
<td>Tick borne illness#</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Emergency Department (ED) visits</strong></td>
<td>46%**</td>
</tr>
<tr>
<td>Medications administered in ED</td>
<td></td>
</tr>
<tr>
<td>Epinephrine (19%)</td>
<td></td>
</tr>
<tr>
<td>Antihistamines (35%)</td>
<td></td>
</tr>
<tr>
<td>Oral Steroids (19%)</td>
<td></td>
</tr>
<tr>
<td>Parenteral Steroids (17%)</td>
<td></td>
</tr>
<tr>
<td>IV Fluids (17%)</td>
<td></td>
</tr>
<tr>
<td><strong>Hospital Admissions</strong></td>
<td>8%</td>
</tr>
</tbody>
</table>

IgE antibody to Alpha-gal in Children (n=51)
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.
Subject #FC02

- sIgE to alpha-gal = 17.6 IU/mL; Total IgE = 184
- Whole blood was collected, fixed & stained
- 3:54 after consuming meat, symptoms began as itching, flushing and progressed: ultimately requiring epinephrine
Subject #FC-07

- sIgE to alpha-gal = 9.3 IU/mL; Total IgE = 204
- Whole blood was collected, fixed & stained
- 6 hours after consuming 56g of pork prosciutto, subject released with (disappointing) mild itch and single hive
Subject #FC-07

Subject calls from car 30 minutes after being released to report progression of itching and “warmth to skin”

Initial picture upon arriving home (approximately 7.5 hours after eating pork prosciutto)
Subject #FC07

Approximately 8.25 hours after eating prosciutto
Subject #FC08

sIgE to alpha-gal = 30.3 IU/mL; total IgE = 146

Before

3hrs 45min after eating meat
Diffuse urticaria appeared at 4hrs 15min after eating meat (left arm shown here)
Why Is Everyone Blaming the Tick?

Geographical distribution of cetuximab hypersensitivity reactions

As reported by O’Neil et al, JCO 2007
Why Is Everyone Blaming the Tick?

Geographical incidence of Rocky Mountain Spotted Fever

Data from CDC website for 2009; accessed 2/2011
Why Is Everyone Blaming the Tick?

Distribution of known cases of delayed anaphylaxis to mammalian meat
Why Is Everyone Blaming the Tick?

Geographical range of *Amblyomma americanum*
Where in the world is Alpha Gal?
Identification of galactose-α-1,3-galactose in the gastrointestinal tract of the tick *Ixodes ricinus*, possible relationship with red meat allergy

Bites from Larval Ticks and IgE to Alpha-gal

<table>
<thead>
<tr>
<th>Test</th>
<th>10/26/06</th>
<th>5/21/07</th>
<th>10/9/07</th>
<th>11/6/07*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab (alphaGal)</td>
<td>0.49</td>
<td>16.9</td>
<td>48.3</td>
<td>130</td>
</tr>
<tr>
<td>Total IgE</td>
<td>127</td>
<td>199</td>
<td>350</td>
<td>532</td>
</tr>
</tbody>
</table>

• Multiple bites by seed ticks are not uncommon in the Southeast.

*Titers: Beef 19.2 Pork 10.1, Cat 17.5, Dog 19.8, IU/ml.
*Chicken, Turkey, Roach, Dust Mite and Ragweed all <0.35 IU/ml.
Time Course of IgE Antibodies to Alpha-gal and Total IgE Following Episodes of Multiple Tick Bites (Red Arrows)

Subject #1

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Alpha-gal Allergy in Arkansas

• Received laboratory results from the only two laboratories that perform Alpha-gal testing

• 627 individuals tested for Alpha-gal from January 2013-September 2015

• 270 tested positive
Age Distribution of Patients with Positive Alpha-gal Tests
Distribution of Patients with Positive Alpha-gal Tests
Patients with Positive Alpha-gal Tests by Season and Year

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Positive Alpha-gal Tests in Arkansas
Distribution of Positive Alpha-gal Tests by County

*Red bars represent the total number of positive patients from County. Percentages represent the percentage of positive patients among total tested from County.
Efforts to Expand Awareness

- Alpha-Gal Taskforce
  - Chaired by State Rep. Julie Mayberry
    - Diverse membership

- Goals
  - Spread general awareness
    - Education of ED docs
    - Education of EMS services
    - Planned education of PCPs
Summary

• An epitope causing allergy to mammalian meat is galactose-alpha-1,3-galactose, and a reaction to this epitope can be delayed.

• There is an association between tick bites and the generation of IgE responses to alpha-gal
  – Generating interest in the field

• Skin testing is not conclusive for this disease and serum tests in combination with history is important.
  – Diagnosis should be considered in those with unexplained anaphylaxis

• Stay tuned
Acknowledgements

- **ACH/ACHRI/UAMS**
  - Dr. Stacie Jones
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  - Dr. Sheva Chervinskiy

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  - Dr. Scott Commins

- **University of Virginia**
  - Dr. Tom Platts-Mills
  - Dr. Peter Heymann
  - Dr. Larry Borish
  - Dr. John Steinke
Questions?