

Allergy to Galactose 1,3- α -galactose (Alpha-gal)

Tina Merritt, MD

Allergy & Asthma Clinic of NWA

Introduction

- 2004 ImClone asked Dr. Platts-Mills to develop a test for severe allergic reactions to Cetuximab (cancer drug)
- ImClone did not get FDA approval, and Martha Stewart got in trouble for insider trading
- 2006, a patient died in Bentonville from the first dose of Cetuximab
- I requested Dr. Platts-Mills develop a new test for this allergy
- Galactose-alpha-1,3-galactose (Alpha-gal) is a carbohydrate expressed on non-primate mammal proteins.

Introduction

- Sensitization to Alpha-gal is hypothesized to lead to anaphylactic allergic response to beef, pork, milk and recombinant proteins used in medical treatments (e.g. Cetuximab)
- These reactions occur more in the mid-southern states, in Virginia, North Carolina, Tennessee, Arkansas, Oklahoma, and Missouri (NEJM)
- The reactions seem to correlate with the distribution of the tick *Amblyomma americanum*, the Lone Star Tick (JACI)

ORIGINAL ARTICLE

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., Sharna M. Satinover, M.S.,
Jacob Hosen, B.S., David Mauro, M.D., Ph.D., Robert 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.

ABSTRACT

BACKGROUND

Cetuximab, a chimeric mouse-human IgG1 monoclonal antibody against the epidermal growth factor receptor, is approved for use in colorectal cancer and squamous-cell carcinoma of the head and neck. A high prevalence of hypersensitivity reactions to cetuximab has been reported in some areas of the United States.

METHODS

We analyzed serum samples from four groups of subjects for IgE antibodies against cetuximab: pretreatment samples from 76 case subjects who had been treated with cetuximab at multiple centers, predominantly in Tennessee, Arkansas, and North Carolina; samples from 72 control subjects in Tennessee; samples from 49 control subjects with cancer in northern California; and samples from 341 female control subjects in Boston.

RESULTS

Among 76 cetuximab-treated subjects, 25 had a hypersensitivity reaction to the drug. IgE antibodies against cetuximab were found in pretreatment samples from 17 of these subjects; only 1 of 51 subjects who did not have a hypersensitivity reaction had such antibodies ($P < 0.001$). IgE antibodies against cetuximab were found in 15 of 72 samples (20.8%) from control subjects in Tennessee, in 3 of 49 samples (6.1%) from northern California, and in 2 of 341 samples (0.6%) from Boston. The IgE antibodies were shown to be specific for an oligosaccharide, galactose- α -1,3-galactose, which is present on the Fab portion of the cetuximab heavy chain.

CONCLUSIONS

In most subjects who had a hypersensitivity reaction to cetuximab, IgE antibodies against cetuximab were present in serum before therapy. The antibodies were specific for galactose- α -1,3-galactose.

From the Division of Hematology/Oncology, Department of Medicine (C.H.C., E.C., J.B., B.A.M.), the Department of Cancer Biology (C.H.C., R.J.S.), and the Department of Otolaryngology (R.J.S.), Vanderbilt University School of Medicine, Nashville; Bristol-Myers Squibb, Plainsboro, NJ (B.M., D.M.); Stanford University School of Medicine, Menlo Park, CA (Q.-T.L.); the Department of Medicine, Duke University Medical Center, Durham, NC (M.M.); Asthma and Allergic Diseases Center, University of Virginia, Charlottesville (S.M.S., J.H., T.A.E.P.-M.); ImClone Systems, Branchburg, NJ (Q.Z., D.J.H.); Channing Institute, Harvard University, Boston (D.G.); and Allergy and Asthma Clinic of Northwest Arkansas, Bentonville (T.H.). Address reprint requests to Dr. Platts-Mills at the Asthma and Allergic Diseases Center, University of Virginia Medical School, Box 801355, Charlottesville, VA 22908, or at tap22@virginia.edu.

Drs. Chung and Mirakhur contributed equally to this article.

N Engl J Med 2008;358:1109-17.

Copyright © 2008 Massachusetts Medical Society.

Amblyomma americanum courtesy of the CDC website



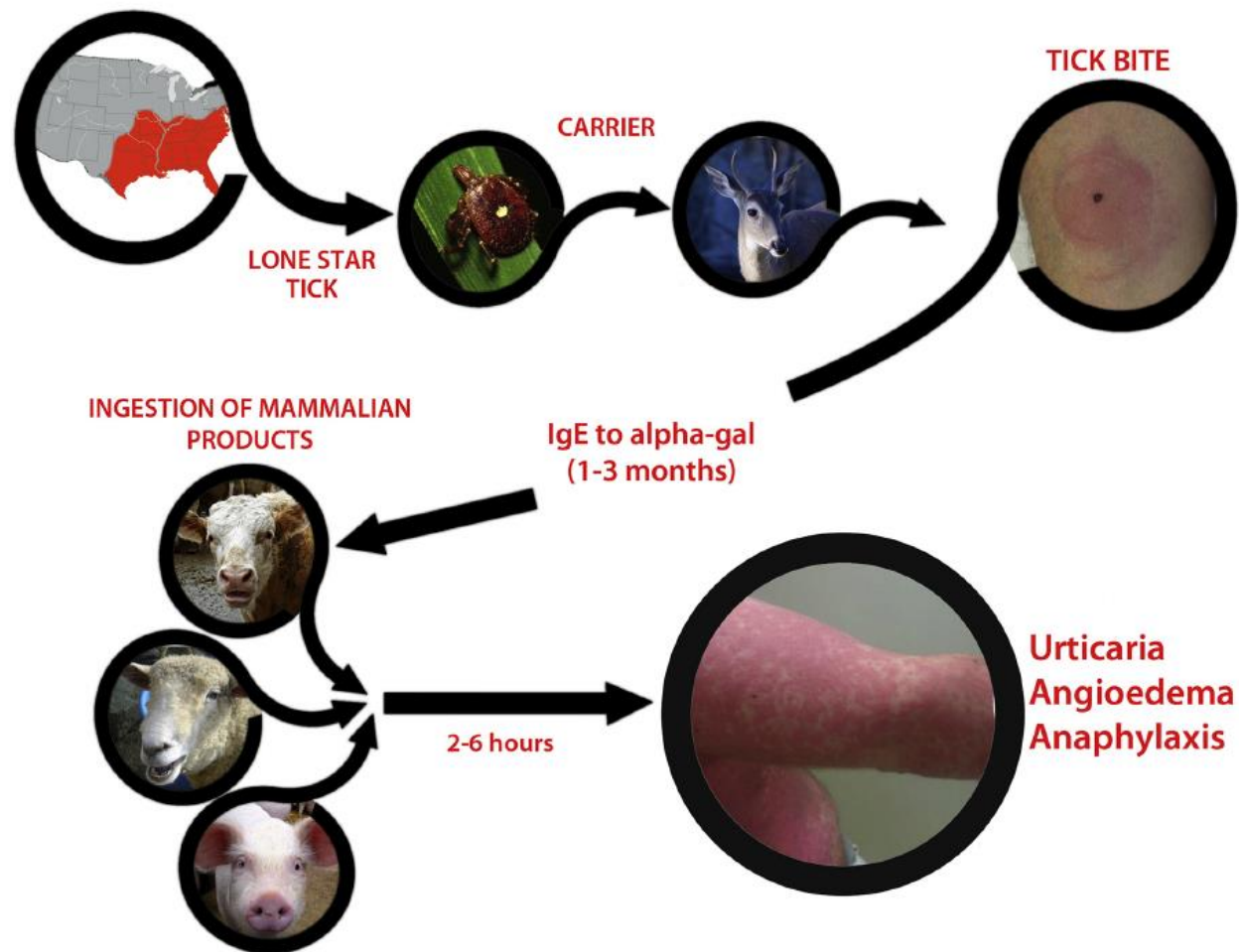
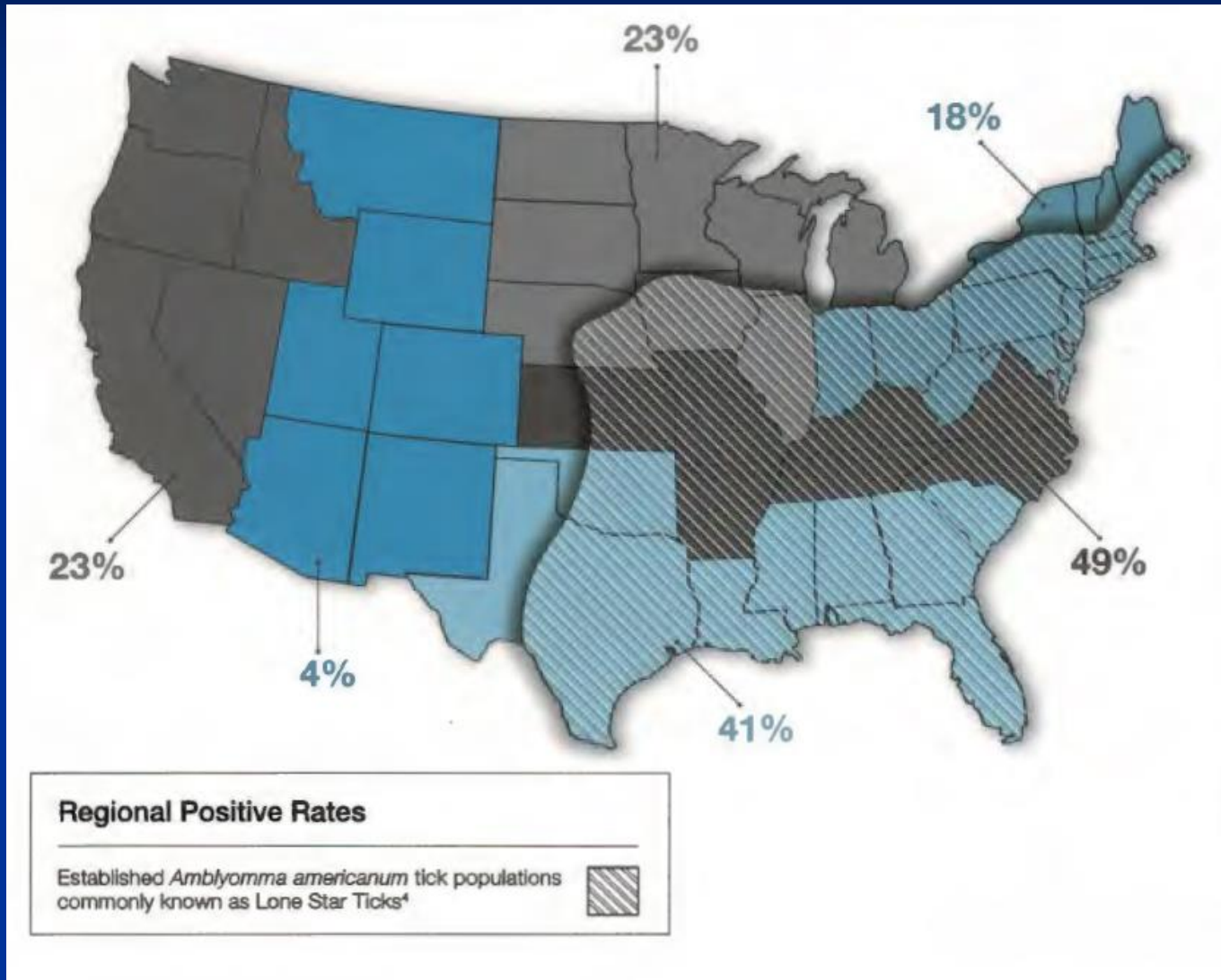
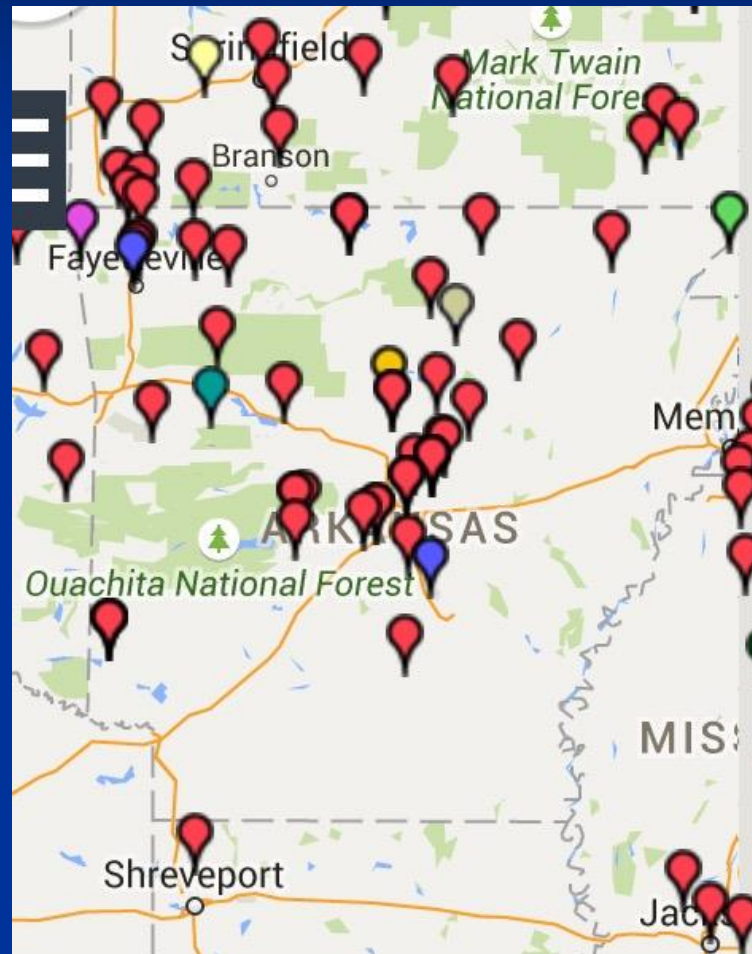


FIG 3. Summary of alpha-gal sensitization leading to clinical symptoms of red meat allergy. The southeastern section of the United States is where most of the reactions to red meat have been reported. This region overlaps with the distribution of the lone star tick. The current hypothesis is that persons are bitten by lone star ticks carried by deer into rural and urban areas. After a period of time, IgE to alpha-gal develops. Once IgE to alpha-gal reaches sufficient levels, ingestion of red meat can trigger reactions. Several of the images used in this figure are licensed under a Creative Commons CC BY-NC 2.0 (Attribution-NonCommercial 2.0 Generic) license (Cow: <https://flic.kr/p/adgjhq> by user Plashing Vole; Deer: <https://flic.kr/p/jeZwq7> by user Cherry Bream; Sheep: <https://flic.kr/p/4WIrD> by user Lauren; Tick: <https://flic.kr/p/cdnNaY> by user Katja Schulz; Pig: <https://flic.kr/p/N7gpc> by user Anne).

(Map and picture courtesy of the ViroCor IBT Laboratories)



Map of Arkansas Alpha-gal support group



Symptoms

- Reactions are usually delayed 2-10 hours
- Hives/rash
- Vomiting/abdominal pain/diarrhea
- Blood pressure drop
- Breathing problems
- Anaphylaxis

Diet Considerations Alpha-gal

- It takes an act of Congress to add a major allergen to food/product labels
- “Natural flavoring” can be mammal.
- Some restaurants add mammal fat to their grease
- Some patients are sensitive to milk, “non-dairy” products can contain casein and whey

Thank you for understanding that my allergy (Mammalian Meat Allergy / Alpha-gal) is life threatening and I need to avoid all mammalian meat and its products.

I CAN eat feathers and fins

Chicken

Turkey

Duck

Quail

Emu

Fish / Shellfish / prawns/ Molluscs /Crocodile

I CANNOT EAT anything mammal

Any raw, cooked or derivatives of-

Lamb

Pork / Bacon / Ham

Rabbit

Kangaroo

Beef

Goat

Buffalo

Veal

Venison

This includes gravies, sauces and foods containing flavour enhancers ~~gelatin~~/glycerin (Jellies, marshmallows)

Dairy.

Milk / Cream / Sour cream / Yoghurt – cow, goat, horse, sheep, buffalo.

Plain, skim, whole, low fat, reduced fat, condensed, evaporated, dried, solids, A2, fat modified.

Butter, buttermilk, margarine

Cheese, all kinds.

Ice cream

Soy

I can eat plant derivatives such as coconut milk/coconut cream, coconut yoghurt, nut milks.

Source: <http://www.tiara.org.au/dietary-information/mammalian-meat-free-diet-guidelines/>
<https://www.allergy.org.au/>

- <http://www.acaai.org>
- <http://www.foodallergy.org>
- <http://www.alpha-gal.org> and www.facebook.com/alpha.gal
- UVA <http://allergytomeat.wordpress.com>
- <http://tinahatley.wordpress.com/2012/8/6/the-alpha-gal>

Conclusions

- In Arkansas thousands of people are positive for IgE to Alpha-gal (beef/pork/gelatin).
- Symptoms include anaphylaxis, urticaria, angioedema, gastrointestinal symptoms and atypical chest symptoms.
- Theories for the increase include rickettsial bacteria in the saliva of regional ticks, increased tick exposure, and exposure to pets.

Disclosures

- Dr. Tina Merritt has interest in the patent for the assay to measure IgE to chimeric monoclonal antibodies at the University of Virginia. PCT/US2008/054113.