Mammalian meat allergy: a diagnostic challenge

Introduction

The first national report in the lay press on galactose-α-1,3-galactose-mediated meat allergy (or red meat allergy) appeared in the German newspaper "Der Spiegel" in December 2012 [1]. Since then, awareness of this clinical picture has increased significantly, not least among affected patients, and it is not infrequent for affected individuals to take the initiative in terms of obtaining a diagnosis. The present report uses the case of an affected female patient as a basis to convey the fundamentals and procedures involved in a disease recognition and diagnosis that has become better understood and more readily diagnosed in recent years, as well as to emphasize the significance of skin tests.

Background

Following the approval of cetuximab – an anti-epidermal growth factor receptor (EGFR) monoclonal antibody used in oncology – in 2006, the first cases of anaphylaxis upon first use of the antibody were seen in the US. Epitopes of the oligosaccharide galactose-α-1,3-galactose (α-Gal) act like an allergen on the humanized antibody cetuximab [2]. This oligosaccharide derives from the mouse in which this antibody was produced and has remained part of the antibody, despite „humanization", since it is spatially close to the variable binding region of EGFR. Since Old World primates and humans lost the ability to produce α-Gal themselves in the course of evolution, the oligosaccharide can have an immunogenic effect in humans. Although it has long been known that humans can produce anti-α-Gal immunoglobulin G (IgG) antibodies in large quantities, the discovery of α-Gal-specific IgE in 2008 was completely new [2]. It was shown as early as in 2009 that anti-α-Gal IgE antibodies can elicit anaphylaxis not only to portions of cetuximab derived from non-primate mammals, but also upon red meat consumption. In this context, symptom onset is comparatively delayed (3–8 h following consumption) and may manifest as urticaria, angioedema or anaphylaxis [3]. Tick bites, which are particularly endemic in the area where cetuximab-induced anaphylaxis and delayed red meat allergy occurred, are suspected to be the trigger of sensitization. The Spiegel article described this development and referred to the first α-Gal patients identified in Germany [1, 4].

Case report

In the weeks following the appearance of the article, Spiegel readers contacted the Department of Dermatology at the Tübingen University Hospital under the assumption that they were affected by the allergy cited in the Spiegel report and subsequently presented for diagnosis. Among these individuals was a 66-year-old female from Baden-Württemberg who, between 2003 and 2006, had repeatedly developed urticaria accompanied by angioedema and anaphylaxis in varying temporal relationship to the consumption of beef, pork, innards, sausage and ravioli. For this reason, allergy diagnosis had been performed at the Dermatological Department in 2006. According to the 2006 medical report, prick testing with prick test solutions for foodstuffs remained unresponsive and total IgE was not elevated at 37 kU/l. However, foodstuffs were additionally tested intracutaneously; tests with solutions for beef, mutton, game, cow milk, cat hair and pharmaceutical gelatin were reactive. Based on these test results, an immediate-type allergy to meat from even-toed ungulates (Artiodactyla) was diagnosed. This order of mammals includes, e. g. cows, swine, camels, sheep and goats. Avoidance of meat from these mammals, as well as products containing gelatin, was recommended. Adherence to this dietary recommendation resulted in no further occurrences of allergic systemic reactions up to 2013. According to the patient history, the patient received four tick bites in the period between 2002 and 2008, but no further bites during the subsequent 5 years [2,3,5]. ImmunoCAP measured specific IgE for α-Gal of 0.12 kU/l and for beef of 0.14 kU/l with a total IgE of 10.4 kU/l. Other meat-related IgE measurements (pork, lactoprotein and cat dander) were undetectable at < 0.1 kU/l. No reaction was seen in skin prick testing with commercially available skin prick test solutions for meat (beef, pork, horse, lamb). Prick-to-prick testing with fresh samples of porcine kidney, pork, bovine kidney and beef showed a one-fold positive reaction with porcine kidney and a questionable reaction with bovine kidney. Intracutaneous testing with gelatin polysuccinate (Gelafundin®) showed no reaction. Animal gelatin also contains α-Gal and can elicit anaphylaxis through exposure to Gelafundin [6], as well as following extensive consumption of gelatin-containing sweets such as jelly babies [7]. Thus, Gelafundin can yield evidence of sensitization in skin testing. It was not possible to repeat the in-

Key words
alpha-Gal – intracutaneous test – galactose-alpha-1,3-galactose, – red meat allergy

Submitted
March 19, 2015

Accepted
March 23, 2015

German version
www.springer-medizin.de/allergo-journal

tracutaneous test that had led to the diagnosis of meat allergy in 2006, since the intracutaneous test solution were originally used was no longer available in Germany in 2013.

Discussion

On the basis of the patient's history and findings, this disease could be classified as α-Gal-mediated meat allergy. It is apparent in retrospect that the allergists dealing with this patient's case back in 2006 had done a remarkable job with their diagnosis of „immediate-type allergy to meat from Artiodactyla" and had been ahead of their time. This case report illustrates how the availability of diagnostic tests influences the diagnostic process. Where an important allergen is already known and available for the serological measurement of specific IgE, or even available as a single allergen, the physician with less experience of allergies can also investigate suspected sensitization in a targeted manner. If, however, the triggering allergen is unknown, the problem needs to be narrowed down by systematically excluding possible allergens. Skin prick and intracutaneous tests in particular have proved to be helpful here in the past. The present case report is a striking example of how skin tests in the hands of experienced allergists make it possible, despite unknown allergens, to detect the problem area effectively and provide appropriate dietary guidance. Test sensitivity is a critical factor here. Commercial skin prick test solutions for meats are not diagnostically reliable for α-Gal-mediated red meat allergy [3, 8]. It can be conjectured that the concentration of α-Gal in these solutions is too low. As own studies as well as US studies show, intracutaneous tests can be very sensitive in α-Gal-mediated red meat allergy and are hence the diagnostic method of choice [6, 8]. Unfortunately, the intracutaneous test solutions described above for various meats have not been available in Germany since 2007. Presumably, increased quality requirements stipulated by the Paul-Ehrlich Institute resulted in the withdrawal of intracutaneous solutions from the market. It is possible that the supplier may have decided differently a year later – after the α-Gal allergen was described for the first time. For the time being, in the case of strong suspicion, there is no choice but to resort to prick-to-prick testing with fresh meat samples, for which personnel requirements are higher, or intracutaneous testing with gelatin-containing infusion solutions [6, 8]. Due to the need to produce tests individually, this forced practice means greater logistical effort for patients and physicians and reduced availability of diagnostic measures. Moreover, these individually produced tests are not able to achieve the same quality and reproducibility of the intracutaneous tests withdrawn for quality reasons since, according to the German Medicines Act, they are always considered a diagnostic investigation in the „isolated case". Thus, adequate standardization is not possible. The discontinuation of intracutaneous testing with meat solutions is therefore a loss in quality and a step backwards in allergy patient care. This gap cannot be fully compensated for by the now CE-certified assay-detecting specific IgE α-Gal for the existing routine diagnosis (α-Gal-rich bovine thyroglobulin as a substrate). Our case report documents how the biological relevance of specific IgE to α-Gal of 0.12 kU/l only became evident as a result of the clinical course and the patient's extremely low total IgE, since the measured titre was close to the 0.1-kU/l cut-off, meaning that here again in vitro serum tests alone would not have yielded the diagnosis. In the context of the greater awareness of this new form of allergy to an oligosaccharide, other clinical phenotypes of meat allergy have now been found. The triggering allergen and its characteristics are as yet unknown or only partially identified [9]. Although this clinical picture is of great interest from both a scientific and a clinical point of view, we are in a poorer position in Germany in 2015 in terms of diagnosing meat allergy using skin tests than we were in 2006.

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Conflict of interest
The authors declare no conflicts of interest.

Cite this as:
Fischer J, Yazdi A, Biedermann T. Mammalian meat allergy: a diagnostic challenge. Allergo J Int 2015;24:81–3
DOI: 10.1007/s40629-015-0050-8

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