

BRIEF COMMUNICATION

Skin prick test and basophil reactivity to cetuximab in patients with IgE to alpha-gal and allergy to red meat

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Abstract

Severe hypersensitivity reactions to red meat with delay of several hours in patients with IgE to alpha-gal (galactose-alpha-1,3-galactose) have been reported. The diagnosis of meat allergy is difficult, because of the limited sensitivity of skin prick tests and specific IgE tests to meat extracts. These circumstances have been explained by the delayed expression of alpha-gal due to digestive processes. Because of the low sensitivity of skin prick tests to meat, we studied the possibility to perform skin prick tests with cetuximab, which carries the alpha-gal epitope. Skin prick and intradermal tests with cetuximab were clearly positive in 2 of 2 patients. As a further diagnostic step, we performed basophil activation tests with cetuximab. Skin prick tests and basophil activation test using cetuximab may be a more sensitive alternative in patients with an assumed allergy to meat.

In recent years, severe hypersensitivity reactions to red meat with delay of several hours in patients with IgE to alpha-gal (galactose-alpha-1,3-galactose) have been identified (1). Alpha-gal is found in all mammalian cells, but not in tissues of humans and Old World monkeys (2). It has been reported that sensitization may occur through tick bites (3–5), parasitic infestations (6), or exposure to cetuximab (7, 8), a chimeric mouse–human IgG1 monoclonal antibody against the epidermal growth factor receptor (approved for use in colorectal cancer and squamous cell carcinoma of the head and neck). Interestingly, cetuximab carries the alpha-gal epitope due to its production in mouse myeloma cell line (9). In daily practice, the diagnosis of meat allergy is difficult, because of the limited sensitivity of skin prick tests and specific IgE tests to meat extracts. Because of the low sensitivity of skin prick tests with commercial and raw meats, we studied the possibility to perform skin prick tests with cetuximab.

Patients and methods

We report on 4 patients (2 women and 2 men, aged 44, 55, 55, and 67 years), of whom 3 suffered from recurrent severe anaphylactic reactions after the ingestion of red meat, typi-

cally with a delay of several hours. Poultry and fish, dairy products, and eggs were tolerated. One patient was sensitized to respiratory allergens (cat and dog dander, house dust mites). A fourth patient had suffered an anaphylaxis upon first exposure to cetuximab. He was not atopic and has had no reactions to meat (Table 1).

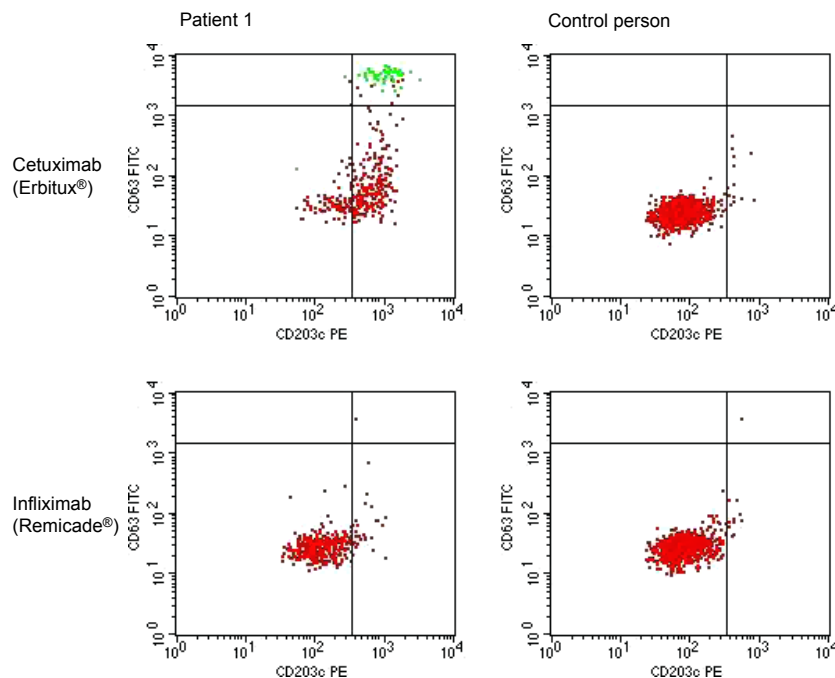
Skin prick tests with commercial meat extracts (Allergopharma, Reinbek, Hamburg, Germany), prick/scratch tests with native meats, skin prick and intradermal tests with cetuximab and infliximab, respectively, rituximab (concentration used for prick test 1 : 1, for intradermal test 1 : 100), determination of specific IgE to meats and alpha-gal (ThermoFisher Scientific, Waltham, MA, USA) were performed. In addition, basophil activation tests with cetuximab and infliximab, respectively, rituximab were carried out. Three patients gave full informed consent. The fourth patient gave only consent for IgE and basophil activation tests.

Results

The first three patients presented with anaphylactic reactions after meat ingestion, and skin prick tests with commercial extracts were negative or equivocal (Table 1). Prick and

Table 1 Results of allergological work-up

	Patient 1 f 55 years	Patient 2 f 44 years	Patient 3 m 67 years	Patient 4 m 55 years
Atopy	No	Respiratory allergens	No	No
Allergic manifestation to alpha-gal	Anaphylaxis several hours after the ingestion of red meat	Anaphylaxis several hours after the ingestion of red meat	Anaphylaxis several hours after the ingestion of red meat	Anaphylaxis upon first cetuximab exposure
SPT with meats	<u>Commercial meats:</u> Beef (+) Pork (+) Lamb (+) Poultry – <u>Native meats</u> Beef – Veal (+) Pork – Lamb – Poultry –	<u>Commercial meats:</u> Beef (+) Pork (+) Lamb (+) Poultry – <u>Native meats</u> Beef – Veal (+) Pork – Lamb – Poultry –	<u>Commercial meats:</u> Beef (+) Pork (+) Lamb (+) Poultry – <u>Native meats</u> Beef – Veal – Pork – Lamb –	nd
Id tests mAbs	Cetuximab positive Rituximab negative	nd	Cetuximab positive Infliximab negative	nd
slgE meats (kU/l)	IgE total: 41.60 kU/l Pork: 1.20 kU/l Beef: 1.90 kU/l Poultry: <0.10 kU/l Lamb: 0.32 kU/l Horse: 0.27 kU/l Rabbit: 0.16 kU/l	IgE total: 13.50 kU/l Pork: 0.82 kU/l Beef: 1.50 kU/l	IgE total: 136.0 kU/l Pork: 0.16 kU/l Beef: 0.33 kU/l Poultry: <0.10 kU/l	nd
slgE alpha-gal (kU/l)	4.2 kUA/l	10.0 kUA/l	5.8 kUA/l	2.13 kUA/l
BADT	Positive to cetuximab Negative to infliximab	Non responder	Positive to cetuximab Negative to rituximab	Non responder

**Figure 1** Basophil activation tests with cetuximab and infliximab in patient 1. Basophil activation test with cetuximab was positive in

patient 1, but negative in a control person. Basophil activation with infliximab as a control turned out negative.

scratch tests with native meats gave weak positive reactions at 20 min. Skin prick tests with other allergens from animal proteins (animal dander) were all negative, except in one patient who was positive for cat and dog dander. Low titers of specific IgE antibodies to red meat extracts were measured; in contrast, specific IgE levels to alpha-gal were 2.1, 4.2, 5.8, and 10.0 kU/l, respectively. Skin prick and intradermal tests with cetuximab were clearly positive in 2 of 2 patients, but negative with rituximab or infliximab. Basophil activation test with cetuximab was positive in 2 patients and negative in 2 non responders (Fig. 1). A control patient without meat allergy was negative in skin prick tests, IgE, and basophil activation.

Discussion

Sensitization to red meat typically manifests with delayed onset of anaphylactic reactions. Therefore, the patient history is often misleading, because often food that was taken shortly before the reaction only is considered. Skin prick tests are also unreliable diagnostic tool, because tests with commercial red meat extracts and with crude red meats are often negative or equivocal. These circumstances and the occurrence of delayed reactions have been explained by the delayed expression of alpha-gal due to digestive processes.

Better results are seen in the detection of specific IgE. Increased levels of specific IgE to red meat were detected in 2 of 3 patients, and in particular, increased IgE titers to alpha-gal in all four patients.

Because of the low sensitivity of skin prick tests with commercial and raw meats, we studied the possibility to perform skin prick tests with cetuximab (10). The tests were clearly positive in 2 of 2 tested patients. Both patients had never

received cetuximab before. As a negative control, we also performed skin prick test and intradermal test with rituximab, respectively, infliximab, which were negative.

As a further diagnostic step, we performed basophil activation tests with cetuximab and as control with rituximab or infliximab, which was positive in 2 patients for cetuximab and negative in 2 non responders. Basophil activation with rituximab or infliximab was always negative.

Conclusion

IgE to alpha-gal, a carbohydrate present in mammalian cells, except in humans and Old World monkeys, may be associated with severe allergic symptoms upon consumption of red meat or upon infusion of cetuximab. Typically, the delay is several hours, implicating a delayed release due to a possible digestion process. Patients with IgE to alpha-gal, as our patient 4, may react upon first exposure to cetuximab, which contains the epitope on the Fab fragment due to the manufacturing process.

The diagnostic possibilities in patients with a putative meat allergy are limited. Skin prick tests with commercial test agents and raw meats are often negative or equivocal. Specific IgE tests to whole meat extracts have also a rather low sensitivity. The more sensitive assay of IgE to alpha-gal is now commercially available; however, it may also be positive in parasitized patients (6). Skin prick tests and basophil activation test using cetuximab may be a more sensitive alternative in patients with an assumed allergy to meat.

Conflicts of interest

The authors have no conflicts of interest.

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