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ORIGINAL ARTICLE

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Relationships between cetuximab-induced anaphylaxis and specific antibodies against allergen and tick-transmitted infections

Chika Namba MD[1] | Mikiko Tohyama MD, PhD[1] | Masamoto Murakami MD, PhD[1] | Tadashi Yoshida MD, PhD[2] | Tohru Ugumori MD, PhD[2] | Naohito Hato MD, PhD[2] | Tomoyuki Tano DDS, PhD[3] | Hiroyuki Hamakawa DDS, PhD[3] | You Kojima MD, PhD[4] | Tomohiro Nishina MD, PhD[5] | Nobuya Monden MD, PhD[6] | Hiromi Fujita PhD[7] | Koji Sayama MD, PhD[1]

[1]Department of Dermatology, Ehime University Graduate School of Medicine, Toon, Japan

[2]Department of Otorhinolaryngology, Head and Neck Surgery, Ehime University Graduate School of Medicine, Toon, Japan

[3]Department of Oral and Maxillofacial Surgery, Ehime University Graduate School of Medicine, Toon, Japan

[4]Gastroenterology and Surgical Oncology, Ehime University Graduate School of Medicine, Toon, Japan

[5]Department of Gastrointestinal Medical Oncology, National Shikoku Cancer Center, Matsuyama, Japan

[6]Department of Head and Neck Medical Surgery, National Shikoku Cancer Center, Matsuyama, Japan

[7]Mahara Institute of Medical Acarology, Anan, Japan

Correspondence
Chika Namba, Department of Dermatology, Ehime University Graduate School of Medicine, Toon, Japan.
Email: chika-n@m.ehime-u.ac.jp

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Abstract

Background: The principal antigen responsible for cetuximab-induced anaphylaxis is galactose-α-1,3-galactose (α-gal), expressed on the Fab portion of the monoclonal antibody. Recent studies have shown that cetuximab allergy is associated with a history of tick bite. We explored factors predicting cetuximab-induced anaphylaxis, focusing on the relationship thereof to a history of tick bite.

Methods: Fifty-two patients prescribed cetuximab at Ehime University Hospital or Shikoku Cancer Center were included in this study. We measured specific immunoglobulin E (IgE) levels targeting red meats, animal danders, and α-gal using immunoCAP. Anti-*Rickettsia japonica* antibody levels were assayed using an indirect immunoperoxidase test. Anticetuximab antibody was quantified by Western blotting and enzyme-linked immunosorbent assay of serum samples.

Results: Of the 52 patients, five exhibited anaphylactic reactions to cetuximab that were not associated with specific IgEs against beef, pork, or animal dander. IgE against α-gal was detected at class 1 in the sera of two of the five patients. Anticetuximab IgE was detected in four of 52 patients, only one of whom had anaphylaxis to cetuximab. Only two of the 52 patients had a history of a tick bite, one of whom had cetuximab-induced anaphylaxis. The patient without anaphylaxis was positive for anti- *R. japonica* antibody.

Conclusions: The α-gal-specific IgE-positivity can be used to identify those at risk of cetuximab-induced anaphylaxis. The cutoff level should be set up the detection limit to predict cetuximab-induced anaphylaxis, because the antibody levels are very low in our study.

KEYWORDS
α-gal, anaphylaxis, cetuximab, red meat, tick bite

1 | INTRODUCTION

Chung et al. (2008) found that immunoglobulin E (IgE) antibodies against cetuximab were present prior to therapy in most patients who developed allergic reactions during cetuximab administration. The antibodies were specific for galactose-α-1,3-galactose (α-gal), which is present on the Fab portion of the cetuximab heavy chain.[1] In 2009, Commins et al reported that patients with IgE antibodies to α-gal experienced delayed anaphylaxis after eating red meat, consistent with the abundant expression of the α-gal epitope in the cells and tissues of nonprimate mammals.[2-4] These authors further suggested that IgE antibodies to α-gal were produced in response to tick bites, because the anti-α-gal IgE antibodies reacted with proteins of *Amblyomma americanum*, a tick species common in the southeastern United States. Thus, IgE antibodies to α-gal produced by repeated tick bites may be associated with the development of anaphylaxis, both during cetuximab infusion and after consuming red meat.[5] High incidences of both cetuximab- and red meat-induced anaphylaxis have been reported in the southern United States, where tick-mediated Rocky Mountain spotted fever is also common.[5,6] In Japan, Chinuki et al. reported a relatively high frequency of cetuximab anaphylaxis in eastern Shimane prefecture, where the prevalence of tick-mediated Japanese spotted fever is also high.[7] In the cited study, specific IgE antibodies against beef, pork, and cetuximab were detected in patients with cetuximab-induced anaphylaxis.[8] Thus, measurement of the levels of IgE antibodies against beef, cetuximab, and α-gal may be useful to avoid cetuximab anaphylaxis in patients given this monoclonal antibody.[8]

As relatively large numbers of tick bite cases are reported in Ehime Prefecture, Japan, we explored whether cetuximab-induced anaphylaxis was associated with the presence of serum antibodies against red meat and/or α-gal. In addition, we measured the levels of antibodies against *Rickettsia japonica*, *Fancisella tularensis*, and severe fever with thrombocytopenia syndrome virus (SFTSV), which cause Japanese spotted fever, tularemia, and severe fever with thrombocytopenia syndrome (SFTS), respectively; these conditions indicate a history of tick bite.

2 | METHODS

2.1 | Patients

Patients admitted to Ehime University Hospital or the Shikoku Cancer Center Gastrointestinal Medical Oncology Department between 2012 and 2014, and who were treated with cetuximab, were eligible for inclusion. All patients gave written informed consent and underwent blood testing. The institutional review boards of both institutions approved the study.

2.2 | Measurement of specific IgE antibodies

The immunoCAP kit (Thermo Fisher Diagnostics, Tokyo, Japan) was used to measure the levels of specific IgE antibodies against beef, pork, chicken, dog and cat dander, and α-gal; the results were grouped into seven classes (0–6). The standard positive cutoff was 0.35 U_A/mL, and the limit of detection was 0.1 U_A/mL. An IgE level <0.35 U_A/mL was graded as class 0, 0.35-0.7 U_A/mL as class 1, 0.7-3.5 U_A/mL as class 2, 3.5-17.5 U_A/mL as class 3, 17.5-50 U_A/mL as class 4, 50-100 U_A/mL as class 5, and >100 U_A/mL as class 6.

Anticetuximab IgE levels were measured using an enzyme-linked immunosorbent assay (ELISA) (Somru BioScience Inc., Charlottetown, PE, Canada), according to the manufacturer's protocol. The cutoff was 0.055, obtained by calculating by the average absorbances of six negative samples and adding two standard deviations to the mean.

2.3 | Antibodies against tick-mediated infectious diseases

We measured antibody titers against *R. japonica*, SFTSV, *F. tularensis*, *Rickettsia typhi*, and *Orientia tsutsugamushi*. *R. typhi*, the causative agent of murine typhus, is transmitted by *Xenopsylla cheopis*, and *O. tsutsugamushi* causes tsutsugamushi disease.

Antibodies to rickettsial and viral antigens were measured using the indirect immunoperoxidase (IP) test.[9,10] The antigen was spotted on a slide, air-dried for 30 min, and then fixed in acetone for 10 min at room temperature. Air-dried antigen-slides were either used immediately or stored at −20°C. Sera initially diluted to 1:40 with 0.01 M phosphate-buffered saline (PBS), pH 7.2, were subjected to serial twofold dilution in microtiter plates. Antigen-bearing slides spotted with 0.01 mL of each dilution were incubated for 30 min at 37°C in a humidified chamber, and washed twice for 5 min in PBS. Following the application of 0.01 mL of 1:100-diluted rabbit anti-human IgG (DAKO Corp., Glostrup, Denmark) to each spot, the slides were incubated for 30 min at 37°C in the chamber, washed twice for 5 min in PBS, and then incubated for 5 min at room temperature in an enzyme substrate solution composed of one volume of 0.2% 4-chloro-1-naphthol in 80% ethanol, four volumes of PBS, and 0.01 volume of 3% peroxide. After three 1-min washes in distilled water, the slides were dried and covered with glycerol gelatin and coverslips. The IP titer was the reciprocal of the highest dilution of serum yielding a blue or blue-black color.

A rapid slide agglutination test was used to titrate antibodies against the causative agent of tularemia, *F. tularensis*.[11] Serial twofold serum dilutions (commencing at 1:10) were spotted onto glass slides (25 μL) and an equal volume of *F. tularensis* antigen solution (5 mg of bacterial suspension/mL of PBS, with 0.5% formalin) was added. After thorough mixing of the reaction by slow rotation of the slides for 3 min, the results were read macroscopically. The final dilution of each serum sample was 1:20.

2.4 | Western blotting

Cetuximab (Bristol-Myers Squibb, Tokyo, Japan) was diluted in buffer to 10 μg/mL and subjected to polyacrylamide gel electrophoresis. The protein was transferred by blotting the gel onto a polyvinylidene

difluoride membrane and reacted with patient sera. Antigen-specific IgE in serum was detected using a peroxidase-labeled anti-human IgE antibody (KPL, Gaithersburg, MD, USA) and an ECL Prime kit (GE Healthcare, Tokyo, Japan).

2.5 | Statistical analysis

Student's *t*-test and Fisher's exact test were used to analyze the results. All analyses were performed with the aid of STATFLEX software (ver. 4.2; ARTEC Inc, Osaka, Japan). A two-sided *P* value <.05 was considered to indicate statistical significance.

3 | RESULTS

3.1 | Baseline patient characteristics

The 52 Japanese patients were enrolled in this study. The mean age of the 52 patients (40 men, 12 women) was 66 years (range: 27–90 years). Blood samples were taken before cetuximab administration in three of the 52 patients, and after administration (range: 1–497 days; median = 14 days, average = 94.5 days) in the remaining 49 patients. Diagnoses were based on the World Allergy Organization guidelines for assessment and management of anaphylaxis.[12] The anaphylaxis guidelines of the Japanese Society of Allergology were used for grading.[13] Anaphylaxis developed in five (four men, one woman) of the 52 patients during the first course of cetuximab (Table 1). Four cases were of grade 3 and one was of grade 2 (Table 1). All five patients then stopped cetuximab therapy. Chlorpheniramine maleate (5 mg) and dexamethasone sodium phosphate (6.6 mg) were given before cetuximab treatment. Of the 52 patients, two had histories of tick bite and one (case 1) developed anaphylaxis to cetuximab (Table 2). Of the five patients developed anaphylaxis to cetuximab, four had B-negative blood and one (case 4) had blood type B (Table 1).

3.2 | Detection of specific IgE antibodies

We measured the serum levels of specific IgE antibodies against beef, pork, chicken, and dog and cat dander. Specific IgE antibodies against pork were not detected in any patient (*P* = 1.00) (Table 3). Specific antibeef IgE antibodies of class 1 and higher were detected in two of the 52 patients, neither of whom had cetuximab-induced anaphylaxis (*P* = .81) (Table 3).

Two patients had specific IgE class 1 antibodies against α-gal; both exhibited cetuximab-induced anaphylaxis (*P* = .0075) (Tables 2 and 3). The other three anaphylactic patients were of specific IgE anti-α-gal class 0. In two of those patients, the levels were over the detection limit but still within the class 0 range (Table 2). The 47 patients who did not have cetuximab-induced anaphylaxis had no specific IgE antibodies against α-gal. Thus, positive antibody status was significantly associated with cetuximab-induced anaphylaxis.

Western blotting was performed to detect specific IgE antibodies against cetuximab, but bands specific for the monoclonal antibody were not apparent in any of the five patients with anaphylaxis. Upon ELISA of serum samples, the average absorbance was 0.034 (0.009-0.13) among the five patients with cetuximab-induced anaphylaxis, compared to 0.04 (0.007-0.73) among the other 47 patients. No significant relationship was apparent between the ELISA titer and anaphylaxis status (*P* = .34). However, among the four patients with positive ELISA results, one (case 2) had cetuximab-induced anaphylaxis.

3.3 | Detection of antibodies against tick-transmitted infections

None of the five patients with cetuximab-induced anaphylaxis had antibodies against *R. japonica*, *F. tularensis*, *R. typhi*, or *O. tsutsugamushi* (Table 4). Of the remaining 47 patients, one had antibodies against *R. japonica* (IgG/IgM; 40/-) and four had antibodies against *R. typhi* (IgG/IgM; 80/1280, 80/-, 80/-, 80/-). However, none of the five patients with antibodies against *R. japonica* or *R. typhi* had a history of tick bite.

4 | DISCUSSION

Cetuximab is a chimeric mouse-human monoclonal IgG antibody against the epidermal growth factor receptor (EGFR), and is approved for use in patients with EGFR-positive unresectable colon and rectal cancer, and head-and-neck cancer. In addition to side effects involving the skin, severe anaphylaxis following first-time administration of the drug has been reported; the frequency is 1.4%–4.5%.[14-18]

TABLE 1 Patients' characteristics and symptoms at the anaphylaxis due to cetuximab

Case number	Age	Sex	Symptom	Fever	Anaphylaxis grade	Period from anaphylaxis to blood sampling	Blood type
1	78	F	Flushing in whole body, hypoxemia, vomiting, Hypotension, feeling faint	–	3	3 weeks	O
2	67	M	Flushing in whole body, hypotension, nausea	–	3	10 months	O
3	76	M	Hypoxemia, hypotension, fecal incontinence, feeling faint	–	3	8 months	O
4	76	M	Urticaria, hypotension	–	2	13 days	B
5	65	M	Flushing in whole body, diarrhea, hypotension, feeling faint, urinary incontinence	+	3	18 days	A

TABLE 2 Specific IgE antibody levels against meat and α-gal and history of tick bite

	Pork		Beef		Chicken		α-gal		
Case number	IgE (UA/mL)	Class	IgE (UA/mL)	Class	IgE (UA/mL)	Class	IgE (UA/mL)	Class	History of tick bite
1	<0.1	0	0.157	0	<0.1	0	0.462	1	+
2	0.132	0	<0.1	0	<0.1	0	0.568	1	–
3	<0.1	0	<0.1	0	<0.1	0	0.167	0	–
4	<0.1	0	<0.1	0	<0.1	0	0.129	0	–
5	<0.1	0	<0.1	0	<0.1	0	<0.1	0	–

TABLE 3 Specific IgE antibodies against meat and α-gal

	Anaphylaxis		
	+ (5 cases)	– (47 cases)	*P* value
Pork	0	0	1.00
Beef	0	2	.81
Chicken	0	4	.69
α-gal	2	0	.0075

TABLE 4 Antibodies against tick-transmitted infection

	Anaphylaxis		
Antibodies	+ (5 cases)	– (47 cases)	*P* value
Rickettsia japonica	0	1	.90
Fancisella tularemia	0	0	1.00
Severe fever with thrombocytopenia syndrome virus	0	0	1.00
Rickettsia typhi	0	4	.66
Orientia tsutsugamushi	0	0	1.00

Antibodies produced against α-gal following a tick bite induce anaphylaxis in patients given cetuximab, the structure of which contains α-gal. Although infliximab, palivizumab, and abatacept also contain the α-gal structure, their interactions with α-gal-specific IgE are not sufficient to elicit an immune response.[19] The Fab domain of cetuximab contains predominantly bi-α-galactosylated bi-antennary complex glycans. Other therapeutic monoclonals contain principally mono-α-galactosylated glycans in the Fc domain; these have a lower affinity for α-gal IgE antibodies than do Fab-domain glycans,[19] explaining the more frequent development of α-gal-specific IgE-induced anaphylaxis following cetuximab administration.

The annual incidence of tick-mediated Japanese spotted fever in Ehime is 12–17 individuals per 1 400 000.[20] In addition, 0.7%–12% of the Japanese population is positive for antibodies against *R. japonica*[21,22]; these individuals live predominantly in areas with high rates of Japanese spotted fever.[23] We therefore speculated that measurement of anti-*R. japonica* antibodies would be useful to verify a history of tick bite. However, we were unable to define the regionality of cetuximab-induced anaphylaxis, or to evaluate the risk of such anaphylaxis by measuring serum antibody titers to tick-transmitted infections.

A significant relationship with cetuximab-induced anaphylaxis was evident only for IgE antibodies targeting α-gal, which were detected in class 1 in two of the five of the patients with anaphylaxis. This association between the detection of specific IgE antibodies and a history of anaphylaxis to cetuximab was significant ($P = .0075$) (Table 3). In addition, specific anti-α-gal IgE antibodies were detected in two of the remaining three patients with anaphylaxis, at levels just above the limit of detection (class 0), whereas no anti-α-gal IgE antibodies were detected in any of the 47 patients who did not develop cetuximab-induced anaphylaxis. Our data suggest that although measurement of α-gal-specific IgE antibodies may be useful to avoid cetuximab-induced anaphylaxis, it may be necessary to increase the sensitivity of the test.

We found that the presence of specific IgE antibodies against beef, pork, and chicken was not significantly related to the development of cetuximab-induced anaphylaxis, although we could not perform the skin tests for beef and pork. Our results differ from those of other groups. Chung et al. reported that five of six patients with cetuximab-induced anaphylaxis had specific IgE antibodies against beef (one of class 1, three of class 2, and two of class 3).[1] Chinuki et al. identified four patients with cetuximab-induced anaphylaxis, two of whom had specific IgE antibodies against beef (one of class 0, one of class 1, and two of class 2).[8] The differences may reflect the low levels of anti-α-gal antibodies in our patients; antibeef and antipork IgE antibodies also react with α-gal. Of the six cases reported by Chung et al, one had class 4, two class 3, and three class 2 levels of anti-α-gal-specific IgE in serum samples.[1] Class 2 or class 3 antibody levels were detected in the four patients described by Chinuki et al.[8] The low anti-α-gal IgE levels noted in our study may reflect induction by a different species of tick. Chinuki et al. used immunoblotting to reveal the presence of α-gal in a salivary gland protein of the tick *Haemaphysalis longicornis*. In Shimane Prefecture, *Haemaphysalis longicornis* is a major vector of *R. japonica*,[24] whereas, in Ehime Prefecture, the vectors are (in order of decreasing frequency): *Haemaphysalis flava*, *Haemaphysalis formosensis*, *Haemaphysalis hystricis*, and *H. longicornis*.[25] The antigenicity of the salivary gland protein may differ among tick types, and the extent of antigenicity may affect the levels of α-gal antibodies induced.

Our study suggested that ELISA-based measurement of anticetuximab antibodies is not useful to prevent anaphylaxis, as three of our patients with anticetuximab IgE antibodies did not develop anaphylaxis following treatment with cetuximab. However, it should be noted that blood samples were taken after, but not before,

cetuximab administration, in these patients. Mariotte et al. measured anticetuximab IgE antibody levels in 92 pretreatment sera, and in the sera of 117 healthy blood donors; anticetuximab IgE was detected in 24 (26.1%) and 33 (28.2%) individuals, respectively.[26] A hypersensitivity reaction to cetuximab developed in 14 of the 92 patients and anticetuximab IgE was detected in 10 (71.4%). This rate was higher than that in patients who did not develop hypersensitivity reactions (14 of 78, 17.9%).[26] It is therefore necessary to review our data while considering pretreatment sera.

The fact that anti-α-gal IgE antibodies were present in two of the five patients with cetuximab-induced anaphylaxis, but not in any patient without anaphylaxis, indicates that the anti-α-gal antibody is an essential contributor to the allergic response. The patient with cetuximab-induced anaphylaxis who lacked the anti-α-gal IgE antibody (case 5) may have experienced an infusion reaction (a frequent complication during the first infusion of a monoclonal antibody[27]), not anaphylaxis. The mechanism underlying the infusion reaction is unclear, but may involve cytokine release and induction of systemic symptoms by mechanisms that differ from those of IgE-mediated hypersensitivity reactions.[27] Although the clinical symptoms of the infusion reaction resemble those of anaphylaxis, the latter is rarely accompanied by fever. Case 5 had a fever of 39°C (Tables 1 and 2), whereas the other four patients had no fever. Measurement of total tryptase and histamine levels can distinguish between anaphylaxis and an infusion reaction,[12] but this was not performed in this patient.

The involvement of factors other than α-gal hypersensitivity in cetuximab-induced anaphylaxis cannot be ruled out. Cetuximab preparations contain the additive polysorbate 80, a known inducer of anaphylaxis. Urticaria has occurred in patients given adalimumab and ustekinumab; eyelid angioedema, rhinitis, conjunctivitis, dyspnea, and wheezing have developed in recipients of the human papilloma vaccine.[28,29] All three drugs contain polysorbate 80. Thus, it is possible that polysorbate caused anaphylaxis in our patient without anti-α-gal IgE antibodies.

In conclusion, cetuximab-induced anaphylaxis may be associated with α-gal hypersensitivity, as suggested by the presence of IgE antibodies in two of our five patients who developed anaphylaxis in response to the drug. In addition, specific anti-α-gal IgE antibodies were detected in two of the remaining three patients with anaphylaxis, at levels just above the limit of detection (class 0), whereas no anti-α-gal IgE antibodies were detected in any of the 47 patients who did not develop cetuximab-induced anaphylaxis. However, the measurement of antibodies against tick-transmitted infectious agents did not yield proof of any relationship between tick bite and cetuximab-induced anaphylaxis. Moreover, anticetuximab antibodies were detected in only one of the five patients with cetuximab-induced anaphylaxis. Our results suggest that measurement of anti-α-gal IgE antibody titers could prevent the development of cetuximab-induced anaphylaxis, but the test sensitivity must be improved.

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CONFLICT OF INTEREST

Nobuya Monden received honorarium from Merk Serono Co., Ltd.

DECLARATIONS

Approval of the research protocol: The institutional review boards of the Ehime University Hospital and Shikoku Cancer Center Gastrointestinal Medical Oncology institutions approved this study.

Informed Consent: obtained.

Registry and the Registration No.: 1303009.

Animal Studies: N/A.

ORCID

Chika Namba http://orcid.org/0000-0002-6307-9516

REFERENCES

1. Chung CH, Mirakhur B, Chan E, , et al. Cetuximab-induced anaphylaxis and ige specific for galactose-α-1, 3-galactose. N Engl J Med. 2008;358:1109–1117.
2. Commins SP, Satinover SM, Hosen J, et al. Delayed anaphylaxis, angioedema, or urticarial after consumption of red meat in patients with IgE antibodies specific for galactose-α-1, 3-galactose. J Allergy Clin Immunol. 2009;123:426–433.
3. Saleh H, Embry S, Nauli A, Atyia S, Krishnaswamy G. Anaphylactic reactions to oligosaccharides in red meat: a syndrome in evolution. Clin Mol Allergy. 2012;10:5.
4. Commins SP, James HR, Stevens W, et al. Delayed clinical and ex vivo response to mammalian meat in patients with IgE to galactose-alpha-1,3-galactose. J Allergy Clin Immunol. 2014;134:108–115.
5. Commins SP, James HR, Stevens W, et al. The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose-α-1, 3-galactose. J Allergy Clin Immunol. 2011;127:1286–1293.
6. Commins SP, Platts-Mills TA. Anaphylaxis syndromes related to a new mammalian cross-reactive carbohydrate determinant. Allergy Clin Immunol. 2009;124:652–657.
7. Chinuki Y, Ishiwata K, Yamaji K, Takahashi H, Morita E. Haemaphysalis longicornis tick bites are a possible cause of red meat allergy in Japan. Allergy. 2016;71:421–425.
8. Chinuki Y, Ito K, Takeda M, Takeuchi K, Takahashi H, Morita E. Four cases of cetuximab-induced anaphylactic shock: possible avoidance of the reaction by prior examination of anti-IgE antibody against galactose-α-1, 3-galactose. Jpn J Dermatol. 2014;124:179–183. (in Japanese).
9. Suto T. Present state of Tsutsugamushi disease in Japan and its early and rapid diagnosis. Clin Virol. 1983;11:23–30. (in Japanese).
10. Fujita H, Sato T, Ohara Y, Homma M. An indirect micro- hemagglutination test for Lyme disease. Microbiol Immunol. 1991;35:589–592.
11. Sato T, Fujita H, Watanabe Y, Ohara Y, Homma M. Microbiological and immunological techniques currently used for the diagnosis of tularemia in the Laboratory of Ohara General Hospital. Ann Rep Ohara Hosp. 1992;35:1–10.
12. Simons FE, Ardusso LR, Bilò MB, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. World Allergy. 2011;4:13–37.
13. Ebisawa M. JSA anaphylaxis guideline-importance of basic management and prevention. Arerugi. 2015;64:24–31. (in Japanese).

14. Saltz LB, Meropol NJ, Loehrer PJ Sr, Needle MN, Kopit J, Mayer RJ. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. J Clin Oncol. 2004;22:1201–1208.
15. Weiss J, Grilley Olson J, Deal AM, et al. Using the galactose-α-1,3-galactose enzyme-linked immunosorbent assay to predict anaphylaxis in response to cetuximab. Cancer. 2016;122:1697–1701.
16. Dupont B, Mariotte D, Dugué AE, et al. Utility of serum anti-cetuximab immunoglobulin E levels to identify patients at a high risk of severe hypersensitivity reaction to cetuximab. Br J Clin Pharmacol. 2017;83:623–631.
17. Kurokawa M, Watanabe Nemoto M, Harada R, et al. Initial experience of radiotherapy plus cetuximab for Japanese head and neck cancer patients. J Radiat Res. 2015;56:849–855.
18. Adams CB, Street DS, Crass M, Bossaer JB. Low rate of cetuximab hypersensitivity reactions in Northeast Tennessee: an Appalachian effect? J Oncol Pharm Pract. 2016;22:784–789.
19. Lammerts van Bueren JJ, Rispens T, Verploegen S, et al. Anti-galactose-α-1,3-galactose IgE from allergic patients does not bind α-galactosylated glycans on intact therapeutic antibody Fc domains. Nat Biotechnol. 2011;29:574–576.
20. Ehime Prefecture [homepage on the internet]. Japan: Ehime Prefectural, [Cited 2016 August 16]. Available from: http://www.pref.ehime.jp/
21. Satoh H, Tsuneki A, Inokuma H, et al. Seroprevalence of antibodies against spotted fever group rickettsia among dogs and humans in Okinawa, Japan. Microbiol Immunol. 2001;45:85–87.
22. Iida H, Ishiguro F, Matumoto K, Kogi K, Kobayashi K, Inada K. A survey of antibodies to spotted fever group amaong human and animals in Fukui prefecture. Ann Rep Fukui Prefect Inst Public Health. 1990;29:79–82. (in Japanese).
23. Chiya S, Takahashi N, Ideguchi S, Suzuki H, Tuboi Y. Prevalence of antibodies to Rickettsiosis of spotted fever group in Kochi. Rep Pub Hlth Kochi 1995;41:24–31. (in Japanese).
24. Tabara K, Kawabata H, Arai S, et al. High incidence of rickettsiosis correlated to prevalence of *Rickettsia japonica* among Haemaphysalis longicornis tick. J Vet Med Sci. 2011;73:507–510.
25. Kan M, Mizota F, Yamashita Y, Hattori M, Ohkura T, Shinomiya H. Investigation of the distribution of ticks in Ehime prefecture. Ann Rep Ehime Prefect Inst Public Health Environ Sci. 2014;17:1–6. (in Japanese).
26. Mariotte D, Dupont B, Gervais R, et al. Anti-cetuximab IgE ELISA for identification of patients at a high risk of cetuximab-induced anaphylaxis. MAbs. 2011;3:396–401.
27. Lenz HJ. Management and preparedness for infusion and hypersensitivity reactions. Oncologist. 2007;12:601–609.
28. Pérez-Pérez L, García-Gavín J, Piñeiro B, Zulaica A. Biologic-induced urticaria due to polysorbate 80: usefulness of prick test. Br J Dermatol. 2011;164:1119–1120.
29. Badiu I, Geuna M, Heffler E, Rolla G. Hypersensitivity reaction to human papillomavirus vaccine due to polysorbate 80. BMJ Case Rep. 2012;2012:bcr0220125797.

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