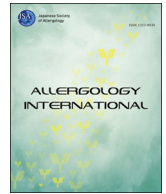




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## Original Article

## Cochineal dye-induced immediate allergy: Review of Japanese cases and proposed new diagnostic chart

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CE cochineal extract

CA carminic acid

SPT skin prick test

## ABSTRACT

**Background:** Cochineal dye is used worldwide as a red coloring in foods, drinks, cosmetics, quasi-drugs, and drugs. The main component of the red color is carminic acid (CA). Carmine is an aluminum- or calcium-chelated product of CA. CA and carmine usually contain contaminating proteins, including a 38-kDa protein thought to be the primary allergen. Severe allergic reactions manifest as anaphylaxis. The aim of this study was to review all Japanese reported cases and propose useful diagnostic chart.

**Methods:** All reported Japanese cases of cochineal dye-induced immediate allergy were reviewed, and newly registered cases were examined by skin prick test (SPT) with cochineal extract (CE) and measurement of CE and carmine-specific serum IgE test. Two-dimensional (2D) western blotting using patient serum was conducted to identify the antigen.

**Results:** Twenty-two Japanese cases have been reported. SPT and the level of specific IgE test indicated that six cases should be newly registered as cochineal dye allergy. All cases were adult females, and all cases except three involved anaphylaxis; 13 cases involved past history of local symptoms associated with cosmetics use. Japanese strawberry juice and fish-meat sausage, and European processed foods (especially macarons made in France) and drinks were recent major sources of allergen. 2D western blotting showed that patient IgE reacted to the 38-kDa protein and other proteins. Serum from healthy controls also weakly reacted with these proteins.

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2D PAGE Two dimensional polyacrylamide  
gel electrophoresis  
BAT basophil activation test

**Conclusions:** SPT with CE and determination of the level of CE and carmine-specific IgE test are useful methods for the diagnosis of cochineal dye allergy.

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## Introduction

Cochineal dye is a natural red colorant extracted from dried female cochineal insects (*Dactylopius coccus*), which are parasites of cacti native to Central and South America, particularly Peru. The main component of the red dye is carminic acid (CA), with a molecular weight of 492 Da. Carmine, which is a hydrated aluminum- or calcium-chelate product of CA, is also used as an insoluble red dye. Both carmine and cochineal dye are used worldwide as coloring agents in foods, drinks, cosmetics, quasi-drugs, and drugs.<sup>1</sup>

Allergic reactions induced by ingestion of processed foods containing cochineal extract (CE) or carmine are believed to be due to insect-derived contaminating proteins rather than CA. A suspected allergen protein is 38 kDa in size.<sup>2</sup>

Several cases of anaphylaxis induced by the intake of foods and drinks containing cochineal dye have been reported by the European Union (EU), prompting it in 2000 to mandate label declarations of potential allergic reaction associated with cochineal dye exposure (mandate E120, which includes CE, CA, and carmine).<sup>3</sup> In 2011, the United States Food and Drug Administration modified its labeling rules regarding indication as to whether CE and carmine are contained in food and cosmetic products.<sup>4</sup> In Japan, CE was approved for use as an existing food additive, according to a 1995 revision of the Food Sanitation Law. In 2011, after several severe cases of anaphylaxis were also reported in Japan, the Consumer Affairs Agency of the Japanese Government called attention to the potential for allergic reactions associated with the use of products containing cochineal dye.

The number of persons suffering from an allergic reaction to cochineal dye reported in the literature is probably an underestimation of the actual incidence because this type of allergy is not well recognized by physicians and because diagnostic methods are not well established. The aim of this study was to review all Japanese reported cases and propose new diagnostic chart. We first analyzed new cases of suspected cochineal dye-induced immediate allergy to propose adequate diagnostic chart. We then reviewed and analyzed all reported Japanese cases of this allergy and compared the data with those reported abroad. Finally, we examined the antigens associated with cochineal dye allergy using two-dimensional (2D) western blotting.

## Methods

### Subjects

All Japanese cases of cochineal dye-induced immediate allergy reported over a 17-year period (1999–2016) were identified from Japanese public databases (the Japan Medical Abstracts Society) and PubMed. New suspected cases from January through March 2014 were registered under “Epidemiological Research related to the Safety of Proteins included in Cosmetics” at the Department of Dermatology, Fujita Health University Hospital, or with us directly. The data from the other new cases, including clinical symptoms, source of cochineal dye, past history, and regional symptoms associated with cosmetics use, were registered between April 2014 and December 2016.

### Ethics

All experiments were performed according to the ethical guidelines of Oita University, Faculty of Medicine (Permit Number: 610; opt-out URL: <http://kenkyu-kokai.wp.med.oita-u.ac.jp/wp-content/uploads/sites/11/2018/02/610.pdf>) and Fujita Health University School of Medicine (Permit Number: HM16-371; opt-out URL: <http://info.fujita-hu.ac.jp/~allergy/research.html>). The study was performed in accordance with the principles embodied in the Declaration of Helsinki.

### Skin prick test (SPT)

A SPT using CE including CA was performed for all patients of newly registered cases as well as healthy volunteers as controls. Informed consent was obtained from all subjects. Samples for the SPT were prepared by us under guidance of the Division of Food Additives, National Institute of Health Sciences (Tokyo, Japan). Dried insects (*D. coccus*) were purchased online (<http://www.cochinealdye.com/index.html>, Birmingham, UK), pulverized with a homogenizer, suspended in 10-fold weight of tap water, and incubated at 80 °C for 15 min in a water bath, with shaking. Color values were measured in the presence of 0.1 N HCl by absorption spectrometry at a wavelength of 490–497 nm, in accordance with the Japanese Standards for Food Additives Handbook.<sup>5</sup> Because the color value of CE in foods and drinks is limited to <0.2 in Japan, samples for SPT were diluted to a color value of 0.1, 0.01, and 0.001 using phosphate-buffered saline (PBS). The protein concentration of SPT samples was measured using a Pierce 660-nm protein assay (Thermo Scientific, Rockford, IL, USA). A color value of 0.1 corresponded to a protein concentration of approximately 0.5 µg/ml. The final prepared samples were sterilized through filtration with 0.2 µm sterilized syringe filter (Steradisc 13, Kurabo, Osaka, Japan) before SPT. The results were evaluated based on criteria used in routine skin tests.<sup>6</sup> The first SPT was performed using a sample with a color value of 0.001, and when negative, the color value was stepped-up to 0.01 and 0.1. In brief, the result was defined as positive when the diameter of the wheal was larger than half of the diameter of the positive control using 10 mg/ml of histamine dihydrochloride (Wako Pure Chemical Industries, Osaka, Japan) or >3 mm.

### Oral challenge test

Oral food challenge with cochineal dye-containing food was performed in several cases in which we could not diagnose the allergy by SPT with CE and CE and carmine-specific IgE test. During the challenge, we monitored patients' blood pressure and oxygen saturation. Small amounts of challenge sample were used at first, and if there were no symptoms, the amount was increased gradually.

### ImmunoCAP assay with CE and carmine

The levels of serum IgE specific to CE and carmine were measured in patients of newly registered cases and healthy volunteers as controls. Informed consent was obtained from all subjects. Levels of IgE specific to a mixture of CE and carmine

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