

Allergic Contact Dermatitis from Carmine

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A 28-year-old woman developed allergic contact dermatitis within 6 to 24 hours exclusively after using carmine-containing eyeshadows and lipsticks. She had both a positive patch test result and a positive antecubital repeated open application test result with carmine 2.5% in petrolatum. Thirty other patients had negative patch test results.

Carmine is a widely used pigment derived from gravid cochineal insects. Carminic acid is the source of its color. Only two previous publications describing allergic contact dermatitis from carmine could be found. The ingredient in carmine causing these delayed hypersensitivity reactions has not been studied.

In contrast, there are numerous reports of immediate hypersensitivity reactions from carmine, mostly from its use in foods and beverages but also from cosmetics and pharmaceuticals. These are immunoglobulin E-mediated reactions directed against cochineal proteins.

COCHINEAL EXTRACT is the concentrated solution produced by the removal of alcohol from an aqueous alcohol extract of dried and pulverized gravid cochineal insects.¹⁻⁴ These insects, mostly *Dactylopius coccus*, parasitize many species of prickly pear cactus (*Opuntia* spp).^{2,4,5} Carmine (Natural Red 4 [CI 75470]) is an insoluble aluminum or calcium-aluminum lake (precipitant) derived from cochineal extract.⁴ It may be processed further to yield a water-soluble powder.⁴

Carmine and cochineal extract may be different shades of red, violet, magenta, or orange, depending on its concentration and its hydrogen ion concentration (pH).^{3,4} The color is due chiefly to carminic acid, a hydroxyanthraquinone linked to a glucose unit.⁴ FD & C grade carmine must contain at least 50% carminic acid.^{1,3} Both carmine and cochineal extract contain residual cochineal insect proteins.^{3,6,7}

Cochineal extract or carmine is used as a colorant in foods, drugs, cosmetics, textiles, inks, paints, and biologic stains.¹⁻⁴ These should not be confused with the chemically unrelated Indigo Carmine (FD & C Blue 2 [CI 73015]) or with Cochineal Red (CI 16255), a synthetic azo dye not approved in the United States for use in foods, drugs, or cosmetics.³

There are at least 18 published reports describing 33 cases of immediate hypersensitivity reactions to carmine,

many of which resulted in systemic anaphylaxis.^{6,8-24} Many other cases have been reported to the United States Food and Drug Administration (FDA).³ In contrast, in a search of the PubMed/MEDLINE, EMBASE, and Scopus databases, the author could find only two previous publications describing delayed hypersensitivity (allergic contact dermatitis) from carmine.^{25,26}

Case Report

A 28-year-old woman of Filipino descent described recurrent dermatitis that usually began within 6 to 24 hours after she used various eye shadows and lipsticks. She had used many of these cosmetics since her teenage years, but she first developed symptoms in her midtwenties. She also had a history of contact dermatitis from costume jewelry and a history of allergic rhinitis but no history of asthma or atopic dermatitis.

She kept detailed records of products that had caused contact dermatitis. These products included a Burt's Bees lip balm and 12 different eye shadows by Estée Lauder, Lancôme, Physicians Formula, M·A·C, and Bare Escentuals. A review of the full ingredient lists of the implicated eye shadows revealed that carmine, iron oxides, and mica were present in nearly all of the products. For this reason, these ingredients were obtained in advance for patch testing. The tested carmine was produced by Sensient Technologies Corporation (Milwaukee, WI).

Patch testing was done on the patient's back with IQ-Ultra Chambers (Chemotechnique Diagnostics, Vellinge, Sweden). Test materials included the 65-allergen North American Contact Dermatitis Group standard series,²⁷

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carmine 2.5% in petrolatum (pet), iron oxides (red, black, and yellow, tested separately) 1% pet, mica 5% pet, and several of the patient's implicated eye shadows. A small amount of petrolatum was mixed with the powdered eye shadows to keep them from falling out of the test chambers. Patch tests were occluded for 48 hours and read at 48 and 120 hours. The carmine (Fig 1), cobalt 1% pet, and nickel sulfate 5% pet patch test sites showed erythema and induration at both readings. The implicated cosmetics gave negative patch-test results.

To verify the clinical relevance of the carmine patch-test reaction, a repeated open application test/provocative use test (ROAT/PUT)²⁸ was performed with a very small quantity of carmine 2.5% pet applied unoccluded twice daily to one antecubital fossa. A few isolated papules first appeared after 12 days of applications. After 16 days, the patient developed semiconfluent papules (Fig 2). She declined additional proposed patch testing or a ROAT/PUT with diluted purified carminic acid.

In the last 3 years, 30 women with eyelid, lip, or facial contact dermatitis who were using carmine-containing cosmetics were patch-tested with carmine 2.5% pet at the Division of Dermatology of the University of California, San Diego. All had negative patch-test results.

In the 3 years since being patch-tested, the patient has used more than a dozen carmine-free eye shadows and lip products and has not had further dermatitis.

Discussion

Carmine was implicated as the allergen in this patient by her contact dermatitis exclusively from carmine-containing lipsticks and eye shadows, a positive patch-test result with



Figure 1. Patch-test result with carmine 2.5% in petrolatum after 120 hours.



Figure 2. Repeated open application test. Carmine 2.5% in petrolatum was applied unoccluded twice daily for 16 days.

carmine 2.5% pet, negative carmine patch-test results in 30 other patients, and a positive antecubital provocative use test with carmine 2.5% pet. For comparison, carmine concentrations used by one major manufacturer range from 0.01 to 4% in lipsticks, 0.05 to 10% in blushes, and 0.02 to 20% in eye shadows (Ken Marenus, PhD, vice president, regulatory affairs, The Estée Lauder Companies, personal communication, June 3, 2008). The nonirritancy of patch testing with carmine 2.5% pet is further supported by the negative results of repeat-insult patch testing with carmine 20% pet in 50 subjects (Brian Jones, PhD, director, research and development, Mary Kay, Inc., personal communication, April 17, 2009).

The false-negative patch-test results on the back of this patient from the same cosmetics that caused contact dermatitis of the lips and eyelids are not unusual. The author has observed this repeatedly with other lip and eyelid cosmetics. It is probably partly a result of regional anatomic variability in percutaneous absorption.²⁹

Two previously published reports describe four patients with delayed hypersensitivity (allergic contact

dermatitis) from carmine; all of the cases were caused by lip products.^{25,26} Three of these cases were documented by patch tests with the lip salve base with and without carmine. In two cases in which carmine patch testing was performed, results with 0.1% concentrations in liquid paraffin²⁵ and in petrolatum were positive.²⁶

In contrast to the rarity of reports of delayed hypersensitivity reactions to carmine, there are at least 33 published descriptions of patients with immediate hypersensitivity to carmine.^{6,8–24} As summarized in recent reports,^{6,24} in 17 of these patients, allergy was caused by occupational exposures, including exposures in carmine manufacturing, cosmetic blending, spice blending in a sausage factory, and among butchers handling additives to sausages, burgers, and salami. Symptoms included asthma, rhinitis, and conjunctivitis. In 16 patients, reactions were non-occupational; many of these reactions were anaphylactic and were mostly due to ingestion of foods or beverages colored with carmine. These included the alcoholic beverage Campari (Gruppo Campari, Milan, Italy),^{11,14,17,23} juices,^{19,23} yogurt,^{12,17,24} artificial crab,^{17,19} fish paste,²² and a popsicle.¹⁵ Many of these patients also described immediate itching, an erythematous eruption, urticaria, or intense rhinorrhea within minutes of their using carmine-containing cosmetics.^{3,11,15,17,19,24} One case was caused by the ingestion of azithromycin tablets.²⁴

These immediate hypersensitivity reactions to carmine are immunoglobulin E-mediated and directed against cochineal proteins.^{6,7,16,18,19,21,23} A major carmine allergen was recently shown to have amino acid sequence homologies with phospholipases, which are known insect allergens.⁷

In contrast, the identity of the allergen causing the delayed hypersensitivity reaction seen in allergic contact dermatitis from carmine has not been determined. Our patient declined further patch testing with purified carminic acid to determine if it was the allergenic ingredient.

Listing of carmine on labels is currently required in the United States for retail-sale cosmetics and over-the-counter drugs but not for foods, cosmetics for professional use only, and free cosmetic samples.³ Owing to concerns about anaphylactic immediate hypersensitivity reactions, the FDA will require disclosure of the presence of carmine or cochineal extract on the labels of all foods and cosmetics, beginning in January 2011.³⁰ The FDA plans to initiate separate rules for prescription pharmaceuticals.³

Summary

This case report has described a patient with allergic contact dermatitis from carmine in numerous cosmetics.

The ingredient in carmine causing these rarely reported delayed hypersensitivity reactions has not been studied. In contrast, there are many reports of immediate hypersensitivity reactions to carmine. These are immunoglobulin E-mediated reactions directed against cochineal insect proteins.

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