

Carmine hypersensitivity masquerading as azithromycin hypersensitivity

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ABSTRACT

Macrolide hypersensitivity is a rarely reported event. However, carmine dye has become increasingly important as a provocative agent. We present a case of a woman with documented carmine hypersensitivity, who reported anaphylaxis 90 minutes after ingestion of a generic azithromycin. Our investigations revealed that this was an allergy to the carmine dye in the tablet's coating rather than to the antibiotic. Seven extracts were prepared including carmine dye, crushed dried female cochineal insects, crushed tablets of Zithromax (Pfizer Inc.) and generic azithromycin (Teva Pharmaceuticals), and the crushed colored coatings from both tablets. These were suspended in preservative-free normal saline, and then applied as a skin-prick test and read at 30 minutes. The skin-prick skin test results were 4+ to histamine and carmine dye, but negative to cochineal insect extract, Pfizer crushed tablets, and negative control. The patient was 1+ to the Teva crushed tablet, but was 4+ to the Teva brand coating and negative to the Pfizer brand coating, which did not contain carmine. The patient subsequently ingested Pfizer Zithromax without any sequelae. To our knowledge, this is the first reported case of carmine anaphylaxis attributed to carmine-containing medication. Careful history and skin-prick testing to the appropriate agents allowed elucidation of the subtlety of the true offending agent without unnecessary avoidance of the medication class. Patients with a carmine hypersensitivity should actively check with their pharmacy or prescribing physician to verify their medications are free of this offending agent.

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Key words: Anaphylaxis, carmine, cochineal extract, cosmetic allergy, dye allergy, food allergy, macrolide allergy, natural colorant allergy, noncertified dye, red dye allergy

CASE PRESENTATION

A 47-year-old woman with history of mild persistent asthma, allergic rhinitis to pollen and dander, and oral allergy syndrome, presented to our clinic for evaluation of facial edema attributed to eating a red raspberry yogurt; swelling of the face and tongue, and respiratory distress attributed to eating red-colored tortellini; and a facial rash and swelling attributed to wearing red eye makeup. It was subsequently discovered that all 3 items contained carmine dye.

Her medications included hydrochlorothiazide, lisinopril, rabeprazole, fluticasone/salmeterol, and albuterol. Allergies included urticaria attributed to sulfa-containing antibiotics. Her past medical history

included hypertension, gastroesophageal reflux, and asthma.

Her baseline spirometry was FVC 3.84 L (107% predicted), FEV₁ 2.9 L (105% predicted), FEF 25–75% of 2.21 L/second (72% predicted), with normal flow loops. Epicutaneous testing to carmine liquid, read at 30 minutes, was 4+ (Wheal 11 mm, Flare 42 mm) with appropriate controls. She was diagnosed with sensitivity to carmine dye, and was counseled about avoidance of carmine-containing products, including how it is labeled on products.

Approximately 45 days later, she was prescribed azithromycin by her primary-care physician for symptoms of an upper respiratory infection. Within 90 minutes of taking the first dose of generic azithromycin (Teva Pharmaceuticals, North Wales, PA) she developed facial itching and eye swelling. She immediately took 50 mg of diphenhydramine and contacted the pharmacy to verify whether the red dye in the medication was carmine. The pharmacist verified that this brand contained carmine, but the Pfizer brand did not. She immediately had a coworker administer her EpiPen (Dey Pharmaceuticals, Napa, CA), and she was

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brought to our office within 15 minutes of her epinephrine dose. She reported previous tolerance to Zithromax (Pfizer Inc., New York, NY).

Physical Exam

Vital signs on arrival were: oxygen saturation of 97% on room air, pulse 108, respirations 14, blood pressure 138/92. Pertinent findings on exam included angioedema of her left upper eyelid, facial erythema and urticaria, but no wheezing audible on auscultation.

Clinical Course

She was given 60 mg of prednisone and observed for 2 hours before being discharged home in stable condition to continue 60 mg of prednisone daily for 3 days along with every 6-hour dosing of diphenhydramine. No symptoms returned.

DIFFERENTIAL DIAGNOSIS

In considering the acute onset of facial angioedema and pruritus in a woman taking an antibiotic, drug allergy was an immediate concern. However, evidence for macrolide hypersensitivity in the medical literature is sparse. Other foods consumed during the course of the day also needed to be considered, as well as angiotensin-converting enzyme inhibitor-induced angioedema. Contact urticaria from a makeup or facial agent was possible, but unlikely given an acute process. Based on a previous diagnosis of sensitivity to carmine, this seemed to be the most likely diagnosis to pursue, given previous tolerance to brand name Azithromycin.

Diagnostic Testing

We performed epicutaneous testing to both the brands Azithromycin (Teva Pharmaceuticals) and Zithromax (Pfizer Inc.) to establish that the reaction was attributable to carmine in the medication covering and not to Azithromycin.

Briefly, one pink-colored 250-mg tablet of each brand was separately crushed and suspended in saline for epicutaneous testing. An additional 250-mg tablet of each brand was stripped of its dye coating with a scalpel, crushed, and suspended in preservative-free saline for testing. Dried female cochineal insects were pulverized and suspended in saline as well (~10 insects in 3-mL saline diluent). These items, and commercial-grade carmine obtained from Warner Jenkinson (St. Louis, MO), histamine (ALK-Abello Laboratories, Round Rock, TX, 0.1 mg/mL), and the saline (Allergy Laboratory Inc., 0.9% saline with 0.03% serum albumin) were applied to her forearm skin. Greer Dust Mite Mix (Greer, Lenoir, NC, 1:20 wt/vol) was also applied to disprove environmental causes.

Epicutaneous testing, checked at 15, 20, and 30 minutes, revealed 4+ reactivity to the Teva coating (wheal

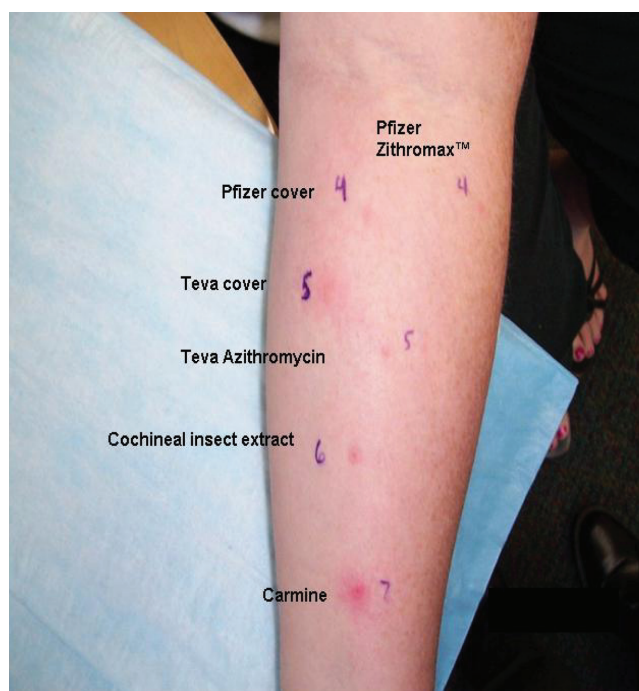


Figure 1. Epicutaneous tests results for azithromycin and carmine.

9 mm, flare 24 mm) and to carmine (wheal 10 mm, flare 29 mm). There was 1+ reactivity to the Teva tablet (wheal 5 mm, flare 8 mm), and no reactivity to Dust Mite Mix, cochineal insect extract, the Pfizer tablet, and the Pfizer coating (Fig. 1). Controls were appropriate. Both carmine and the Teva reactivity developed between 20 to 30 minutes, as has been typical of our experience with carmine.

DISCUSSION

Macrolide hypersensitivity has been rarely reported.^{1,2,3,4} However, carmine dye has become increasingly important as a provocative agent in hypersensitivity to a number of carmine-containing products.^{5,6,7} Carmine is a red color derived from the *Dactylopius coccus costa* insect that grows on the prickly pear cactus. It is also referred to as cochineal extract.^{5,8,9,10,11} The color is produced from the aqueous-alcohol extract of the dried, gravid female insect, and consists of 10% carminic acid, plus the residual insect body.¹¹ Carmine has been approved by the Food and Drug Administration (FDA) as a noncertified dye for use in foods and drugs since 1967, and in cosmetics since 1977.¹² It is the only biogenic dye allowed for use in cosmetics around the eye. As a noncertified color, carmine/cochineal extract does not have to be specifically declared on food product labels, and can be referred to generically as "color added", "artificial color added", or "carmine color".^{12,13} However, its presence is required to be declared in all cosmetics except for professional-use-

Table 1. Known Cases of Carmine Hypersensitivity

Author and Year	Sex	Exposure Route	Reaction	Occupation	Positive Test	Type	Notes
Sarkany et al. 1961 ¹⁶	3 pts	cutaneous-lip salve	contact dermatitis		Yes	Patch test	First known report in medical literature
Burge et al. 1979 ⁶	M, M	inhalation	bronchospasm	factory workers			
Park et al. 1981 ¹⁷	M	cutaneous-lip stick	anaphylaxis	soldier		Bronchial challenge	
Tenabene et al. 1987 ¹⁸	F, M, M	inhalation	bronchospasm	spice/food handlers	Yes	Epicutaneous, bronchial challenge	
Quirce et al. 1994 ¹⁸	M, F, M	inhalation	bronchospasm	dye factory workers: manufacturer (M), cleaning staff (F), ex-worker(M)	Yes	Epicutaneous, <i>vitro</i> IgE, bronchial challenge	
Kägi et al. 1994 ²⁰	F	ingestion-Campari-Orange	anaphylaxis		Yes	Epicutaneous, <i>vitro</i> IgE	First reported case from ingestion
Beaudouin et al. 1995 ⁷	F	ingestion-fruit flavored yogurt	anaphylaxis		Yes	Epicutaneous, basophil histamine release	
Stücker et al. 1996 ²¹	F	inhalation	bronchospasm	food factory worker	Yes	Epicutaneous, <i>vitro</i> IgE	
Wüthrich et al. 1997 ²²	F, F, F, F, F	ingestion-alcoholic beverage	anaphylaxis		Yes	Epicutaneous, <i>vitro</i> IgE	
Baldwin et al. 1997 ²³	F	ingestion-red popsicle	anaphylaxis		Yes	Epicutaneous, <i>vitro</i> IgE (P-K)	
Acero et al. 1998 ²⁴	M	inhalation and ingestion	bronchospasm, rhinoconjunctivitis	spice factory packer, non-manufacturing	Yes	Epicutaneous, immunoblot, bronchial challenge	
DiCello et al. 1999 ²⁵	F, F	ingestion-artificial crabmeat, fruit flavored yogurt	anaphylaxis		Yes	Epicutaneous	
Lizaso et al. 2000 ²⁶	M, F, F	inhalation	bronchospasm	dye plant worker, dye plant clerical worker, dye plant chemist	Yes	Epicutaneous, immunoblot, bronchial challenge	

Table 1. Continued

Author and Year	Sex	Exposure Route	Reaction	Occupation	Positive Test	Type	Notes
Chung et al. 2000 ¹¹⁵	F, F, F	ingestion	anaphylaxis		Yes	Epicutaneous, immunoblot	No patient sera recognized the same protein bands. Sera also recognized cochineal insect.
Tabar et al. 2003 ²⁷	F, F	inhalation	bronchospasm	dye factory clerical worker, dye factory laboratory worker	Yes	Epicutaneous, immunoblot, bronchial challenge	
Anibarro et al. 2003 ²⁸	M, M	inhalation	bronchospasm	both butchers	Yes	Epicutaneous, immunoblot, bronchial challenge	
Ferrer et al. 2005 ²⁹	M	inhalation	bronchospasm	spice blender	Yes	Epicutaneous, <i>in-vitro</i> IgE immunoblot, bronchial challenge	
Greenhawt et al. Present Case	F	ingestion and topical-generic azithromycin, fruit flavored yogurt, colored pasta, eye makeup	anaphylaxis, local rash and angioedema	office worker	Yes	Epicutaneous	This is the first case report of exposure from a pharmaceutical source.
FDA MedWatch ¹³	F	ingestion-Tropicana Ruby Red Grapefruit Juice; topical-purple eye shadow	anaphylaxis; skin rash		Yes	Epicutaneous	Test positive to the grapefruit juice, Good and Plenty candy, eye shadow
FDA MedWatch ¹³	F	ingestion-custard style strawberry banana yogurt	anaphylaxis		Yes	Epicutaneous	Test positive to the yogurt

Table 1. Continued

Author and Year	Sex	Exposure Route	Reaction	Occupation	Positive Test	Type	Notes
FDA MedWatch ¹³	F	ingestion–SoBe fruit juice	anaphylaxis				Cochineal extract was declared on the bottle label
FDA MedWatch ¹³	F	ingestion–Crab soup, yogurt, candy, Ruby Red Grapefruit Juice, pasta salad with artificial crab meat	anaphylaxis		Yes	Epicutaneous	
FDA MedWatch ¹³	F	ingestion–gelatin based desert	eyelid angioedema				
FDA MedWatch ¹³	F	ingestion–custard style yogurt, multiple cosmetics	anaphylaxis (to the ingestion)				
FDA MedWatch ¹³	NA	NA	NA				
FDA MedWatch ¹³	NA	ingestion–yogurt	anaphylaxis		Yes	Epicutaneous	
FDA MedWatch ¹³	F	ingestion, topical–neither specified	NA				
FDA MedWatch ¹³	F	topical–eyeliner	NA				

M = male; F = female; FDA = The United States Food and Drug Agency; NA = not available.

only products and free samples.¹³ Under the FDA Modernization Act of 1997, all inactive ingredients in over-the-counter medications for oral consumption, including noncertified colors, must be declared.^{13,14,15} Presently, this does not apply to prescription drugs, but the FDA is planning to formally recommend similar recommendations for the declaration of inactive ingredients, including noncertified colors.¹³ The Center for Science in the Public Interest has successfully petitioned the FDA to reconsider the present labeling regulations for carmine/cochineal extract and require its declaration in all products.¹³

Since 1961, there have been ~35 known case reports in the medical literature and FDA MedWatch program of allergic reactions to carmine in food and cosmetic products^{5-7,16-29} (Table 1). To our knowledge, this is the first reported case of carmine sensitivity from its use as a pharmaceutical dye. Sensitization has been thought to occur through a topical route via cosmetics, and through occupational exposure to carmine powder dust in European dye factory workers.²⁹

Because there is residual biogenic contamination in commercial carmine, it has been theorized that insect protein is responsible for the clinical allergy to carmine.^{5,22,24,25,29} It is unknown exactly how much insect protein contamination exists in commercial preparations of carmine used in food, cosmetic, or pharmaceutical dye. Furthermore, its use in products is elusively disclosed, creating a dangerous situation for carmine-sensitive patients. Several investigative groups have shown that carmine allergy is IgE-mediated, *via* epicutaneous tests, Prausnitz-Küstner tests, *in vitro*-specific IgE, and immunoblot/inhibition analysis. Unfortunately, there has been no universal pattern of recognition among these studies, and there remains no conclusive evidence that cochineal insect biogenic protein is the major allergen.^{5,22,24,25,28,29} Though there is no conclusive evidence to this point, it is believed that the processing of cochineal to carmine creates a haptenized particle with residual insect-body protein that is presumably the source of the hypersensitivity.

At our center, in performing a workup of a patient with suspected carmine hypersensitivity, we first confirm a suspected reaction involving a red-, purple-, or pink-colored food and try to identify any commercial product involved. Epicutaneous testing to other foods and pollen agents is performed before carmine testing when appropriate. When carmine is tested, we apply liquid carmine as a standard epicutaneous test and do not read the test until 30 minutes after application. It has been our experience over the past 10 years that this antigen is associated with late-developing test results. We do not routinely test to cochineal extract.

Final Diagnosis

Carmine hypersensitivity.

CONCLUSION

Carmine/cochineal extract is a known allergen that is used as a dye in foods, drugs, and cosmetics. Because it is a noncertified color, in most situations it does not have to be explicitly labeled, creating a dangerous situation for the carmine-sensitive patient. Many patients give a history of previous intolerance to carmine-containing foods. It is widely suspected that some biogenic protein contaminant in carmine is the major antigen, though this has not been definitively proven. The protein may be altered through processing into a more allergenic form, accounting for the negative skin tests to cochineal insect themselves. Providers need to have a high index of suspicion even if carmine does not appear on the label of the suspected product. Epicutaneous tests should be observed for 30 minutes because the reactivity often develops after 20 minutes. Carmine allergy has now been reported from use in foods, cosmetics, and drugs.

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ERRATUM

In “A case of hydrocortisone desensitization in a patient with radiocontrast-induced anaphylactoid reaction and corticosteroid allergy,” *Allergy and Asthma Proceedings*, 27:265–268, the correct name for the senior author is Evans R. Fernandez-Perez, M.D., M.S.

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