Received: 8 May 2022 | Accepted: 30 May 2022

DOI: 10.1002/cia2.12261

Journal of Cutaneous Immunology and Allergy

WILEY

CASE STUDY

Immediate hypersensitivity reaction to carboxymethylcellulose in lidocaine jelly and dimethicone drops: A case report and mini-review

Eri Hotta MD, PhD | Risa Tamagawa-Mineoka MD, PhD | Yuri Onishi MD | Ayaka Sotozono MD | Megumi Kusunoki MD | Junko Hattori MD | Natsue Ioka MD | Hiromi Mizutani MD, PhD | Koji Masuda MD, PhD | Norito Katoh MD, PhD

Department of Dermatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Correspondence
Eri Hotta and Risa Tamagawa-Mineoka
Department of Dermatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, 465, Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan.
Emails: h0tta@koto.kpu-m.ac.jp; risat@koto.kpu-m.ac.jp

Abstract

Excipient allergies are rare and difficult to diagnose. Carboxymethylcellulose (CMC, carmellose sodium) is an anionic water-soluble polymer derived from native cellulose, that is, used as an excipient. Here, we report a case of urticaria caused by the CMC in lidocaine jelly and dimethicone drops, which had used for upper gastrointestinal endoscopy. CMC is widely used in pharmaceutical preparations, food additives, and other pharmaceuticals, and its use is increasing. However, there are few reports on immediate hypersensitivity reactions because substances containing CMC. Previous reports and our case suggest that excipients, such as CMC, can be potential hidden allergens.

KEYWORDS
carboxymethylcellulose, dimethicone drops, immediate hypersensitivity reaction, late-onset reaction, lidocaine jelly, oral intake

1 | INTRODUCTION

Carboxymethylcellulose (CMC, carmellose sodium), which is derived from native cellulose, is widely used as a suspending agent in pharmaceutical preparations, food products, and cosmetics.[1] However, there are few reports about immediate hypersensitivity reactions to substances containing CMC.[2–13] Here, we report a case of urticaria caused by CMC, which was present in lidocaine jelly and dimethicone drops that had been used for upper gastrointestinal endoscopy.

2 | CASE REPORT

A 70-year-old Japanese male, who had a history of prostatic hyperplasia, but no allergies to medicines or other commonly used substances was referred to our hospital to undergo an examination to determine the cause of his urticaria. Five months earlier, he had undergone upper gastrointestinal endoscopy. He had previously undergone upper gastrointestinal endoscopy twice before (1 and 2 years ago) but had not experienced any allergic reactions, such as urticaria, after these procedures. About 1 h after the upper gastrointestinal

Hotta and Tamagawa-Mineoka contributed equally to this work.

endoscopy, he developed urticaria on his trunk and limbs without any reduction in his blood pressure, diarrhea, or dyspnea. Lidocaine jelly (2% Xylocaine® jelly, which contained methylparaben, propylparaben, CMC, and a pH adjuster), midazolam (which contained midazolam, a pH adjuster, and a stabilizing agent), pronase (Pronase MS®, which contained pronase, hydroxypropyl cellulose, HPC, and lactose), sodium bicarbonate (which contained sodium bicarbonate and dimethylpolysiloxane), and dimeticone (2% Gascon® drops, which contained dimeticone, polysorbate, sorbitan monostearate, CMC, silicon dioxide, ethanol, methyl parahydroxybenzoate, dibutylhydroxytoluene, saccharin sodium hydrate, and aromatic chemicals) were used for the upper gastrointestinal endoscopy. Drug-induced urticaria was suspected.

Open application tests were performed with lidocaine jelly and saline (as a negative control) on the forearms. The patient exhibited negative reactions to the open application tests after 15 min. Prick tests of the drugs and latex gloves used for the upper gastrointestinal endoscopy were performed on the forearms; that is, the effects of midazolam, pronase (4% aq.), sodium bicarbonate (4% aq.), dimeticone drops, lidocaine jelly, and latex were tested. The responses were examined at 15 min after the application of the test substances, and the mean largest diameter and associated perpendicular diameter of the wheals were recorded. Prick tests were also performed with saline as a negative control and histamine (10 mg/ml) as a positive control. Evaluation of prick test results was performed as previously reported.[14] The allergen wheal of similar size as that of histamine was given a relative size of 3+, if double the size of histamine 4+, and if half the size of histamine 2+. A positive result was defined as ≥2+. In addition, a positive reaction was defined as when the response to the test substance was at least 3 mm greater than that of the negative control. The prick tests with lidocaine jelly produced a positive reaction (2+) (Figure 1A) and those (2+) with dimethicone drops (Figure 1B). All of the other substances produced negative results. Based on these findings, the patient was diagnosed with urticaria caused by the lidocaine jelly and dimethicone drops. CMC and paraben were present in both substances.

Then, we examined which components of lidocaine jelly had induced the allergic reaction. Therefore, we first examined whether lidocaine was the causative allergen; that is, we performed prick tests with lidocaine-free jelly (Caine Zero® jelly, which contained distilled water, glycerin, propylene glycol, hydroxyethyl cellulose, trehalose, methyl parahydroxybenzoate, and propyl parahydroxybenzoate) and 1% lidocaine hydrochloride injections (1% Xylocaine® injections, which contained lidocaine hydrochloride, sodium chloride, and a pH adjuster) and intradermal tests with 1% lidocaine hydrochloride injections (0.1 and 1% aq.), 1% lidocaine hydrochloride injections with epinephrine (1% Xylocaine® injections with epinephrine, which contained lidocaine hydrochloride, sodium chloride, a pH adjuster, hydrochloric acid, methylparaben, sodium pyrosulfite, and adrenaline), and saline (as a negative control). The patient exhibited negative reactions to the prick tests and intradermal tests after 15 min. Then, we performed administration

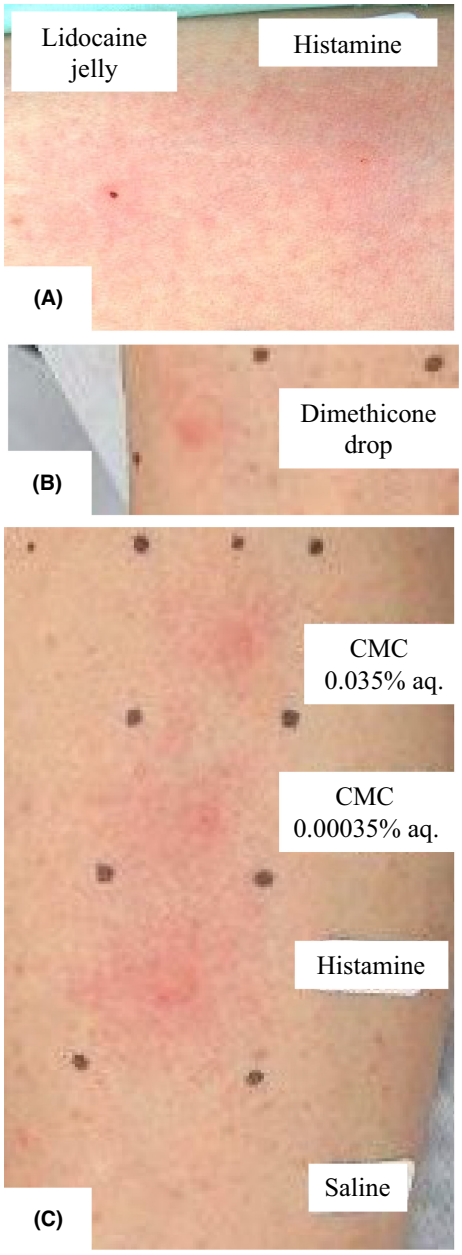

FIGURE 1 Responses to the prick tests of lidocaine jelly, histamine (A), dimethicone drops (B), CMC (0.00035% and 0.0035% aq.), histamine, and saline (C) were observed at 15 min

tests with 1% lidocaine hydrochloride injections and 1% lidocaine hydrochloride injections with epinephrine (0.5 mL each). The patient demonstrated negative reactions to the administration tests. Thus, we determined that lidocaine was not the causative allergen responsible for the urticaria.

Next, we performed skin tests with the components of lidocaine jelly. In previous studies, prick tests of CMC, methylparaben, and propylparaben were performed beginning with the following low concentrations: CMC: 0.00075% aq.,[3] methylparaben: 0.12% aq., and propylparaben: 0.012% aq.[15] The concentrations of CMC, methylparaben, and propylparaben in the lidocaine jelly were 3.5%, 0.06%, and 0.03%, respectively, but those of the

TABLE 1 Summary of CMC-containing substances

Route of administration	Products containing CMC	
Injections	Corticosteroid	Triamcinolone acetonide (Kenacort-A®)
	Local anesthetics	Lidocaine (Xylocaine Viscous®)
	Luteinizing hormone-releasing hormone formulation	Leuprorelin acetate (Leuplin®)
Oral medicine	Corticosteroid	Prednisolone (Predonine®)
	Antifungal agent	Miconazole nitrate (Florid Oral Gel®)
	Anti-inflammatory agent	Sodium azulene sulfonate (Azulene®, Atenelen®)
	Gastric medicine	Itopride hydrochloride (Ganaton®)
	Constipation drug	CMC-Na (Balkose®), Dimeticone (Gascon®)[a]
Topical preparations	Corticosteroid	Fluticasone furoate (Allermist®), Mometasone furoate hydrate (Nasonex®), Triamcinolone acetonide (Aftach®, Kenalog®)
	Local anesthetics	Lidocaine (Xylocaine® jelly)[a]
Contrast agents	Barium sulfate	Sodium bicarbonate

[a]The causative agents in the present case.

dimethicone drops were unknown. Therefore, we performed prick tests with methylparaben (0.001% and 0.01% aq.), propylparaben (0.001% and 0.01% aq.), CMC (0.00035% and 0.0035% aq.), saline (as a negative control), and histamine (10 mg/ml) (as a positive control). The prick tests with CMC (0.00035% and 0.0035% aq.) produced a positive reaction (2+) within 15 min (Figure 1C). All of the other substances produced negative results. The prick tests with CMC (0.0035% aq.) did not produce any reactions in three normal subjects. We did not perform prick tests with the components of the dimethicone drops because the only components found in both the lidocaine jelly and dimethicone drops were CMC and paraben. Based on these findings, the patient was diagnosed with urticaria because the CMC in lidocaine jelly and dimethicone drops.

Moreau et al.[12] indicated that cross-reactions can occur between CMC and methyl hydroxyethylcellulose (MHEC). So, we also performed prick tests with MHEC, hydroxypropylcellulose, cellulose (0.00035%, 0.0035%, 0.035%, 0.35%, and 3.5% aq.; Wako, Japan), and histamine (10 mg/ml) (as a positive control). All of these substances produced negative results, indicating that the patient had been sensitized to CMC. Subsequently, the patient avoided any foods containing CMC, and he no longer developed urticaria.

3 | DISCUSSION

CMC is an anionic water-soluble polymer derived from native cellulose.[1] It is increasingly being used in pharmaceutical preparations (Table 1); cosmetics; and foods, such as ice creams, chocolate products, frozen cakes, and condiments, in which it is used in food additives to promote the solubilization of compounds with poor water solubility and emulsifiers. There have been several reports on immediate hypersensitivity reactions to the CMC in corticosteroid injections containing triamcinolone acetonide,[2–8] food additives,[9,11] barium sulfate,[10] or white chalk[12] in the English literature (Table 2). In the cases involving corticosteroid injections containing triamcinolone acetonide,[2–8] urticaria and anaphylaxis developed approximately 30 min after the injection. On the other hand, in the previous cases[9–11] and our case immediate hypersensitivity reactions to orally consumed CMC, such as that present in foods, barium sulfate, lidocaine jelly, or dimethicone drops, occurred after 30 min to 4 h. Interestingly, *Bigliardi* et al.[3] reported that three patients who had developed anaphylaxis caused by the CMC in local injections of corticosteroid preparations demonstrated negative results in oral provocation tests of CMC (136–250 mg). CMC is hardly decomposed or absorbed in the gastrointestinal tract and is inert; therefore, sensitization and allergic reactions rarely occur after its ingestion.[9] In our case, the patient may have become sensitized to CMC in foods or the pharmaceutical preparations used for the upper gastrointestinal endoscopy although he had not experienced any allergic reactions in daily life, even though he had consumed foods, such as jam or ice cream, containing CMC. These findings suggest that some special conditions, such as the long fasting period imposed before gastrointestinal endoscopy examinations, may make allergic reactions to CMC more likely. In addition, a greater number of encounters with orally consumed CMC-containing substances, such as foods or pharmaceutical preparations, may be required to induce allergic reactions to CMC. CMC is being increasingly used in our daily lives; therefore, physicians should carefully assess patients' CMC intake in cases involving episodes of anaphylaxis or urticaria of unknown cause that occur in daily life.

TABLE 2 Summary of data of detailed published cases

Case	Age	Gender	Causative agent	Route of administration	Time to onset	Symptoms	Prick test results of CMC	Intradermal skin test results of CMC
1[2]	26	Male	Triamcinolone acetonide	Injection	Within 15 min	Anaphylaxis	Not done	0.0002% aq.; positive, 0.002%aq.; positive
2[3]	76	Female	Triamcinolone acetonide	Injection	30 min	Anaphylaxis	0.00075% aq.; negative	0.0000075% aq. positive
3[3]	37	Male	Triamcinolone acetonide	Injection	30 min	Anaphylaxis	0.001% aq.; negative	0.0001% aq. positive
4[3]	59	Male	Betamethasone	Injection	30 min	Anaphylaxis	0.00075% aq.; equivocal	0.0000075% aq. positive
5[4]	48	Male	Triamcinolone	Injection	2 h	Anaphylaxis	0.00001–0.1%; positive	Not done
6[5]	24	Male	Triamcinolone acetonide	Injection	Immediately	Anaphylaxis	0.1% aq.; positive	Not done
7[6]	74	Female	Triamcinolone acetonide	Injection	Within 10 min	Anaphylaxis	0.0001% aq. 0.001% aq.; positive	Not done
8[7]	67	Female	Triamcinolone acetonide	Injection	Within 20 min	Anaphylaxis	Concentration unknown; positive	Not done
9[8]	45	Female	triamcinolone acetonide	Injection	Within 30 min	Anaphylaxis	Concentration unknown; positive	Not done
10[9]	14	Female	Food additives	Oral intake	Within 4 h	Anaphylaxis	5% aq.; positive	Not done
11[10]	63	Female	Barium sulfate	Oral intake	30 min	Anaphylaxis	1.2% aq.; positive	Not done
12[11]	57	-	Food additives	Oral intake	45 min	Anaphylaxis	Concentration unknown; positive	Not done
13[12]	17	Female	White chalk	Contact	Within a few min	Contact urticaria	0.1% aq.; positive	Not done
14[13]	44	Male	Eye drops	Contact	Immediately	Urticaria, angioedema	0.5% aq.; positive	Not done
15[a]	70	Male	Lidocaine jelly, dimethicone drop	Contact, oral intake	1 h	Urticaria	0.00035% aq., 0.0035% aq.; positive	Not done

[a]Present case.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

DECLARATION SECTIONS

Approval of the research protocol: No human participant was involved in this study. Dr. Norito Katoh is a member of the Journal of Cutaneous Immunology and Allergy Editorial Board. Management of the peer review process, and all editorial decision making, for this article was undertaken by Editor in Chief.

Informed consent: N/A.

Registry and the registration no: N/A.

Animal studies: N/A.

ORCID

Risa Tamagawa-Mineoka https://orcid.org/0000-0001-9379-9584

REFERENCES

1. Hollabaugh CB, Burt LH, Walsh AP. Carboxymethylcellulose. Uses and applications. Ind Eng Chem. 1945;37:943–7.
2. Patterson DL, Yunginger JW, Dunn WF, Jones RT, Hunt LW. Anaphylaxis induced by the carboxymethylcellulose component of injectable triamcinolone acetonide suspension (Kenalog). Ann Allergy Asthma Immunol. 1995;74(2):163–6.
3. Bigliardi PL, Izakovic J, Weber JM, Bircher AJ. Anaphylaxis to the carbohydrate carboxymethylcellulose in parenteral corticosteroid preparations. Dermatology. 2003;207(1):100–3.
4. García-Ortega P, Corominas M, Badia M. Carboxymethylcellulose allergy as a cause of suspected corticosteroid anaphylaxis. Ann Allergy Asthma Immunol. 2003;91(4):421.
5. Laing ME, Fallis B, Murphy GM. Anaphylactic reaction to intralesional corticosteroid injection. Contact Dermatitis. 2007;57(2):132–3.
6. AAl H, van Maaren M, Vermes A. Anaphylactic reactions following Kenacort-A® injection: carboxymethylcellulose is involved once again. Contact Dermatitis. 2011;64(3):179–80.
7. Niwa Y, Hayama K, Tagui T, Ito-Watanabe M, Endo T, Fujita H, et al. Case of anaphylaxis due to carmellose sodium. J Dermatol. 2020;47(1):e15–7.
8. Townsend K, Laffan J, Hayman G. Carboxymethylcellulose excipient allergy: a case report. J Med Case Reports. 2021;15(1):565–8.
9. Ohnishi A, Hashimoto K, Ozono E, Sasaki M, Sakamoto A, Tashiro K, et al. Anaphylaxis due to carboxymethylcellulose: add food additives to the list of elicitors. Pediatrics. 2019;143(3):e20181180.
10. Muroi N, Nishibori M, Fujii T, Yamagata M, Hosoi S, Nakaya N, et al. Anaphylaxis from the carboxymethylcellulose component of barium sulfate suspension. N Engl J Med. 1997;337(18):1275–7.
11. Brockow K, Bauerdorf F, Kugler C, Darsow U, Biedermann T. "Idiopathic" anaphylaxis caused by carboxymethylcellulose in ice cream. J Allergy Clin Immunol Pract. 2021;9(1):555–7.
12. Moreau L, Alomer G, Dubé N, Sasseville D. Contact urticaria from carboxymethylcellulose in white chalk. Dermatitis. 2006;17(1):29–31.
13. Carbonell A, Miralles JC, Escudero AI, Martínez A, Pineda F, Aldana D. Urticaria-angioedema due to carboxymethylcellulose eye drops. J Investig Allergol Clin Immunol. 2012;22(4):288–9.
14. Tamagawa-Mineoka R, Masuda K, Yagami A, Nakamura M, Sato N, Matsunaga K, et al. Food-induced anaphylaxis in two patients who were using soap containing foodstuffs. Allergol Int. 2018;67(3):427–9.
15. Fisher AA. Allergic paraben and benzyl alcohol hypersensitivity relationship of the "delayed" and "immediate" varieties. Contact Dermatitis. 1975;1(5):281–4.

How to cite this article: Hotta E, Tamagawa-Mineoka R, Onishi Y, Sotozono A, Kusunoki M, Hattori J, Immediate hypersensitivity reaction to carboxymethylcellulose in lidocaine jelly and dimethicone drops: A case report and mini-review. J Cutan Immunol Allergy. 2022;5:217–221. doi:10.1002/cia2.12261