Original Article

Radiocontrast Media Hypersensitivity: Skin Testing Differentiates Allergy From Nonallergic Reactions and Identifies a Safe Alternative as Proven by Intravenous Provocation

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What is already known about this topic? Nonallergic hypersensitivity upon injection of iodinated radiocontrast media (RCM) is not rare and can be prevented by premedication. Full-blown anaphylaxis or maculopapular exanthem has been increasingly reported to be caused by RCM allergy.

What does this article add to our knowledge? Intradermal testing of 1:10 dilutions of the original RCM solution enables differentiation between nonallergic reactions, immediate-type RCM allergy, or delayed-type RCM allergy. Provocation testing regularly identifies an alternative RCM, which can be used in future X-ray examinations.

How does this study impact current management guidelines? Cross-reactivity between different RCM is common, but intravenous provocation with skin test–negative RCM is safe and reliably identifies a tolerated alternative. Iodine allergy is a rare but possibly underestimated cause of RCM-induced maculopapular exanthem.

BACKGROUND: Hypersensitivity reactions occurring within minutes after intravascular injection of iodinated radiocontrast media (RCM) are not rare and have been previously considered to be nonallergic. However, in the last decades, evidence is increasing that genuine RCM allergy may present as either full-blown anaphylaxis or delayed exanthematous skin reaction.
OBJECTIVES: We aimed to assess whether allergy diagnostics including skin and provocation testing can differentiate between nonallergic and allergic RCM hypersensitivity by identifying the causative RCM as well as tolerated alternative RCM.
METHODS: We retrospectively evaluated clinical and diagnostic data from 45 consecutive patients with RCM hypersensitivity.
RESULTS: Immediate nonallergic RCM hypersensitivity was diagnosed in 21 patients, immediate-type RCM allergy in 11, delayed-type RCM allergy in 11, and delayed-type iodine allergy in 2. All patients with immediate-type RCM allergy had a history of moderate to severe anaphylaxis. Eleven of 13 patients with delayed-type allergic reactions including the 2 cases of iodine allergy suffered from maculopapular exanthem developing several hours to days after exposure, 1 was a systemic hypersensitivity syndrome, and 1 a fixed drug eruption. Of 18 RCM-allergic patients tested, all tolerated an alternative RCM in the intravenous provocation.
CONCLUSIONS: The diagnostic sensitivity of intradermal RCM testing to identify allergic patients is high in both immediate-type and delayed-type RCM allergy. Intravenous provocation with a skin test–negative RCM is safe and enables identification of a tolerated alternative RCM. Additional skin testing of iodine solution is required to identify patients with iodine allergy. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: *Anaphylaxis; Provocation testing; Drug adverse reaction; Drug allergy; Drug hypersensitivity; Exanthem; Radiocontrast media*

INTRODUCTION

Nonallergic (not IgE-mediated) hypersensitivity reactions following intravenous injection of iodinated radiocontrast media (RCM) are not uncommon, though the incidence has considerably declined because of the introduction of modern nonionic and low-osmolar RCM.[1] In recent years, increasing evidence shows that genuine (IgE-mediated) RCM allergy is comparatively rare, but is a potential cause of severe clinical reactions and should therefore be diagnosed reliably. Immediate-type, IgE-mediated allergy may be the underlying mechanism of RCM-induced anaphylaxis, whereas delayed-type RCM allergy usually manifests as maculopapular exanthem (MPE) occurring within hours or even days after exposure.[2-5]

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Abbreviations used
DRESS- Drug rash with eosinophilia and systemic symptoms
MPE- Maculopapular exanthem
RCM- Radiocontrast media

Intradermal testing of diluted RCM solutions is a sensitive test method for the diagnosis of both immediate-type and delayed-type RCM allergy.[6,7] Published data on the diagnostic sensitivity of intradermal RCM testing, however, considerably differ, ranging from less than 50% to more than 90%.[7-11] The specificity of intradermal tests with appropriate dilutions, that is, at least 1:10, of the original RCM preparation is likewise considered to be very high; thus, provocation is recommended with skin test−negative RCM only.[6] Patients and laypersons commonly perceive RCM-induced adverse reactions to be equivalent to an iodine allergy. True iodine allergy, however, has been diagnostically confirmed as a cause of RCM-induced MPE on only rare occasions and has even been referred to as "iodine allergy myth."[12,13]

Clinical and diagnostic data from a cohort of 45 consecutive patients with a convincing history of an RCM-induced immediate- or delayed-type hypersensitivity reaction were retrospectively evaluated for the current study. (1) We aimed to accurately differentiate between reactions due to nonallergic mechanisms, immediate-type allergy, and delayed-type allergy. (2) Skin tests were evaluated to identify the culprit and possibly cross-reactive RCM as well as patients reacting to iodine. (3) Provocation testing was performed as the gold standard to assess the validity of skin tests as well as to evaluate its ability to identify an alternative RCM, which can be used in future X-ray examinations.

METHODS

Patients

RCM hypersensitivity was diagnosed in 45 patients between January 2008 and August 2018. Collection of data included age and sex, type of radiological examination, and time interval between RCM injection and onset of symptoms. Clinical symptoms were assigned to reaction patterns, that is: (1) immediate-type anaphylaxis-like reaction within 15 minutes or (2) delayed-type reaction more than 6 hours after RCM injection. The severity of anaphylaxis was classified as mild, moderate, or severe as explained in Table I.[14] We only recruited patients with at least 1 objective symptom of anaphylaxis, that is, generalized urticaria. Unlike previous studies, cases with merely subjective or minor immediate-type reactions, such as itching, flushing, nausea, palpitations, or heat sensation, were excluded. Information about the clinical reaction was retrieved from medical records, radiologists, treating physicians, and caregivers when necessary. We additionally recorded the time interval between the clinical reaction and presentation for allergy testing. The institutional review board of the University Hospital Würzburg consented to the retrospective review and publication of anonymized clinical data.

Intradermal RCM testing

Intradermal testing of RCM solutions was performed according to Brockow et al[6] and invariably included readings at 15 minutes and on days 2, 3, and 4. At least 3 RCM (which are most commonly used by the radiologists in the geographical region of our allergy center) including the culprit RCM were tested in a 1:10 dilution of the original RCM preparation in physiological saline solution. This dilution was always prepared directly before the testing procedure and used within a maximum of 1 hour. We injected 30 to 50 μL of the test solution to produce a bleb of 3 to 5 mm. A wheal of at least 6-mm diameter with surrounding erythema at 15-minute reading was assessed as a positive immediate reaction. Wheals measuring 3 to 5 mm in diameter were considered irritative if subsiding on testing at a dilution of 1:100. An erythematous and infiltrated plaque, clearly visible and palpable on days 2, 3, and 4, was assessed as a positive delayed-type skin test reaction.

Iodine skin testing

In cases with a history of RCM-induced delayed-type MPE, prick and patch tests with iodine tincture (iodine dissolved in a mixture of ethanol and water, resulting in a solution containing ~18-22 mg/mL iodine and 21-26 mg/mL sodium iodide) and 2% Lugol's solution (6.6 mg/mL iodine and 13.4 mg/mL potassium iodide in an aqueous solution) were performed in addition to RCM intradermal testing.[15] Prick and patch testing was performed and read as described by Brockow et al[6] and Scherer et al.[12] Clinical relevance of a positive prick or patch test reaction was verified by repeated open application of the aforementioned iodine solutions twice daily for 5 days onto the outer side of an upper arm.

Intravenous RCM provocation

Provocation with a skin test−negative RCM was performed to exclude RCM allergy and to determine the reliability of a negative skin test result. General principles of our provocation protocol were as follows: (1) the time interval since immediate-type reactions was at least 4 weeks, and recovery from MPE was at least 8 weeks ago; (2) written informed consent was obtained from each patient; (3) before RCM injection, renal function and thyroid function were examined by measurement of serum creatinine and thyrotropin; (4) intake of metformin was discontinued 48 hours before RCM injection[16,17]; (5) patients were closely monitored and equipment for emergency treatment was available throughout the entire procedure. Incremental doses were given intravenously every 30 minutes. Patients with a history of anaphylaxis received 0.05, 0.5, 1.0, 5.0, 7.5, 10.0, and 25.0 mL (total 49.05 mL). Patients who reported a delayed-type reaction received 1.0, 5.0, 7.5, 10.0, and 25.0 mL (total 48.5 mL). All patients were observed for at least 1 hour after the last injection and were advised to present for objective examination if any symptoms developed within the next days.

RESULTS

Clinical data

Nonallergic RCM hypersensitivity was diagnosed in 21 patients, immediate-type allergy in 11, and delayed-type allergy in 13 (Table II and Figure 1). RCM were most commonly administered during urography (15×), coronary angiography (14×), or computed tomography (14×). Table II presents baseline clinical data including the patients' age and sex, incriminated RCM, time interval to onset of symptoms, and clinical signs. The time interval between the RCM-induced hypersensitivity reaction and presentation for allergy testing was less than 1 year in 37 of 45 evaluated patients (82.2%).

All 11 patients with immediate-type RCM allergy had a history of moderate to severe anaphylaxis, which occurred within 5 minutes after RCM injection. In contrast, 20 of the 21 patients with nonallergic hypersensitivity reported only a mild cutaneous

TABLE I. Grading the severity of anaphylaxis

Severity	Symptoms
Mild: predominately skin and subcutaneous tissue are affected; negligible to minor systemic symptoms	Generalized urticaria with or without angioedema, throat tightness, tachycardia, mild abdominal discomfort
Moderate: features of considerable respiratory, cardiovascular, or gastrointestinal involvement	Dysphonia or hoarseness, deep cough or wheezing, hypotension (systolic blood pressure <90 mm Hg in adults), abdominal cramps, vomiting, somnolence, confusion, impaired vision
Severe: hypoxia, shock, and severe neurological compromise	Stridor, cyanosis, loss of sphincter control, syncope (loss of consciousness), respiratory and cardiac arrest

TABLE II. Patient cohort

Clinical parameters	Nonallergic (not IgE-mediated) hypersensitivity (n = 21)	Immediate-type (IgE-mediated) allergy (n = 11)	Delayed-type (T- cell–mediated) allergy (n = 13)
Males/females	5/16	4/7	6/7
Age (y), median (range)	55 (20-79)	61 (46-77)	58 (44-80)
Radiological examination			
Coronary angiography	3	6	5
Computed tomography	7	2	5
Urography	10	3	2
Phlebography	1	0	1
Incriminated RCM			
Iopamidol	0	1	1
Iopromide	7	4	0
Iomeprol	10	6	9
Iobitridol	4	0	1
Iohexol	0	0	1
Iodixanol	0	0	1
Latency time from RCM administration to first symptoms			
<1 min	4	1	NA
1-5 min	10	10	NA
6-15 min	7	0	NA
6-12 h	NA	NA	4
1-2 d	NA	NA	7
3 d	NA	NA	2
Clinical signs			
Delayed skin reaction			
Maculopapular exanthem	NA	NA	11
Systemic hypersensitivity (DRESS)	NA	NA	1
Fixed drug eruption	NA	NA	1
Anaphylaxis			
Mild	20	0	NA
Moderate	1	6	NA
Severe	0	5	NA
Time interval between RCM-induced reaction and allergy testing			
<6 mo	5	8	10
6-12 mo	10	2	2
>1-5 y	6	1	1

NA, Not applicable.

reaction, that is, generalized urticaria. The total 21 skin test–negative patients with nonallergic reactions received a medical document recommending that premedication should be administered before application of iodinated RCM.[18]

Of the 13 patients with delayed-type reactions, 11 suffered from MPE. One patient (#LA-9, Table III) was diagnosed with drug-induced hypersensitivity syndrome or drug rash with eosinophilia and systemic symptoms (DRESS) due to a generalized pustular exanthem, facial erythema and edema, fever, and hepatitis (maximal glutamate-pyruvate transaminase, 736 U/L). Photographic records of circumscribed, erythematous, and bullous lesions on the dorsal hands and feet compatible with a

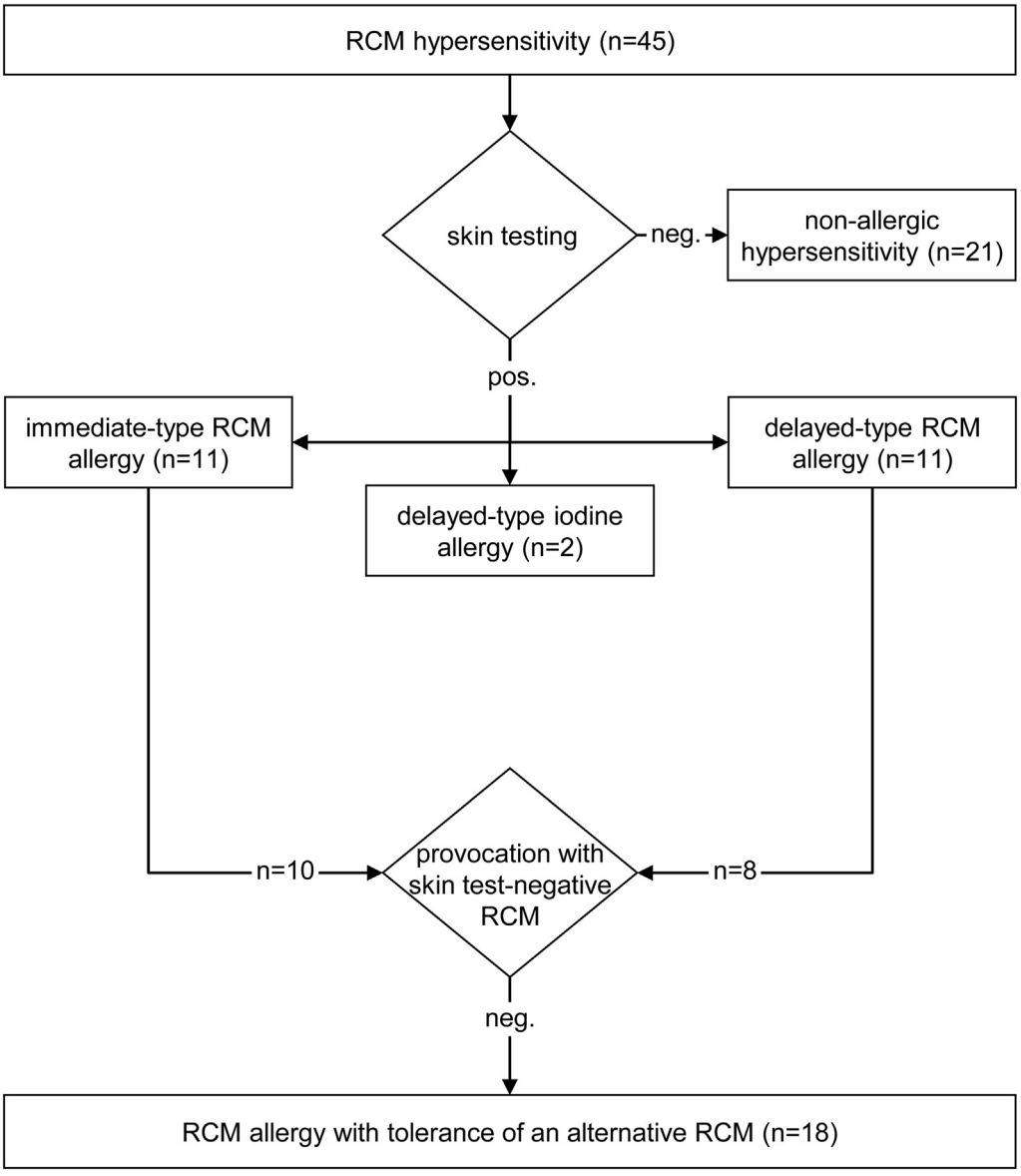

FIGURE 1. Results of allergy testing in 45 patients with RCM hypersensitivity. *Neg.*, Negative; *pos.*, positive.

multilocular fixed drug eruption were available in another patient (#LA-6, Table III), and postinflammatory hyperpigmentation of these lesions was still visible at the time of testing. Diagnosis of these clinical variants of nonimmediate drug reactions was based on established clinical and laboratory criteria.[19,20]

Intradermal RCM testing

Test results of the 22 patients with RCM allergy are presented in Table III. In late readings at days 2, 3, and 4, all intradermal test results were either clearly positive or negative. Wheal-and-flare reactions at 15 minutes were also almost always unequivocally positive, with a wheal diameter of at least 6 mm and surrounding erythema. A borderline test reaction measuring 4 to 5 mm was found in the reading at 15 minutes in only 2 cases when using standard 1:10 dilutions of iopromide and iopamidol, respectively. Subsequent testing of a 1:100 dilution was clearly negative and the initial test reactions were thus considered as irritant or false positive.

Three RCM, namely, iopamidol, iopromide, and iomeprol, were tested in all patients because they are most commonly used by the referring radiologists within our geographical region (Table III). We observed a certain degree of cross-reactivity between iopromide and iomeprol, whereas sensitization against iopamidol occurred either isolated (#IM-5, #LA-10) or in patients with broad sensitization to several RCM (#LA-1, #LA-5). An isolated iomeprol allergy was found in 7 cases, and 1 patient was exclusively sensitized against iopromide (#IM-8). There was a tendency toward a broader sensitization pattern among patients with delayed-type reactions compared with those with immediate reactions.

In the patient reporting an iobitridol-induced fixed drug eruption (#LA-6), diagnostic intradermal testing with RCM was positive only within the areas of former lesions.

TABLE III. Results of skin and provocation testing

Patient	Incriminated RCM	Clinical reaction*	Intradermal skin testing†‡						Tolerated intravenous provocation
			Iopamidol	Iopromide	Iomeprol	Iobitridol	Iohexol	Iodixanol	
Cases with immediate-type RCM allergy									
#IM-1	Iopromide	Severe	−	+	−	+	−	−	Iomeprol
#IM-2	Iopromide	Severe	−	+	+	−	−	−	Iopamidol
#IM-3	Iopromide	Severe	−	+	+	−	−	−	Iopamidol
#IM-4	Iomeprol	Severe	−	+	+	−	−	−	Iopamidol and iobitridol
#IM-5	Iopamidol	Moderate	+	−	−	ND	ND	ND	ND
#IM-6	Iomeprol	Moderate	−	−	+	−	−	−	Iopamidol
#IM-7	Iomeprol	Moderate	−	−	+	−	+	−	Iobitridol
#IM-8	Iopromide	Severe	−	+	−	−	ND	ND	Iobitridol
#IM-9	Iomeprol	Moderate	−	+	+	−	−	−	Iopamidol
#IM-10	Iomeprol	Moderate	−	−	+	ND	ND	ND	Iopamidol
#IM-11	Iomeprol	Moderate	−	−	+	−	−	−	Iopamidol
Cases with delayed-type RCM allergy									
#LA-1	Iomeprol	MPE	+	+	+	−	+	+	ND
#LA-2	Iomeprol	MPE	−	+	+	ND	ND	ND	ND
#LA-3	Iodixanol	MPE	−	−	−	ND	ND	+	Iopamidol
#LA-4	Iomeprol	MPE	−	−	+	ND	ND	ND	Iopromide
#LA-5	Iohexol	MPE	+	+	+	−	+	+	Iobitridol
#LA-6	Iobitridol	Fixed drug eruption	−	+	−	+	ND	ND	Iopamidol
#LA-7	Iomeprol	MPE	−	−	+	ND	ND	ND	Iopamidol
#LA-8	Iomeprol	MPE	−	−	+	−	ND	ND	ND
#LA-9	Iomeprol	Systemic hypersensitivity	−	−	+	ND	ND	ND	Iopromide
#LA-10	Iopamidol	MPE	+	−	−	ND	ND	ND	Iomeprol
#LA-11	Iomeprol	MPE	−	+	+	ND	ND	ND	Iomeprol

MPE, Maculopapular exanthem; *ND*, not done.
*Severity of anaphylaxis.
†Wheal-and-flare reaction at 15 min in cases with immediate-type RCM allergy.
‡Red infiltrated plaque at days 2-4 in cases with delayed-type RCM allergy.

Cases of iodine allergy

Two patients had a clear-cut history of MPE approximately 12 hours after injection of iomeprol during coronary angiography and computed tomography, respectively. Alternative causes including viral or bacterial infections or other drugs could be ruled out. Unexpectedly, intradermal testing result including that with the culprit RCM was consistently negative. Prick testing of iodine tincture, however, revealed an unequivocally positive, erythematous, and infiltrated skin reaction on days 3 and 4 in both patients. Prick testing result with 2% Lugol's solution was negative. Subsequent open epicutaneous application of iodine tincture twice daily for 5 days provoked an acute allergic contact dermatitis. Additional oral provocation with Lugol's solution was rejected by both patients. Skin testing results with these iodine solutions were invariably negative in all other 11 patients with a history of RCM-induced MPE.

Intravenous RCM provocation

Of the 22 patients with RCM allergy, all 18 tested patients tolerated intravenous provocation with a skin test−negative RCM (Figure 1; Table III). Iopamidol was identified as a tolerated alternative in 10 patients, iomeprol and iobitridol were tolerated in 3 patients each, and iopromide in 2 (Table III). Patient #IM-4 tolerated iopamidol in the context of controlled provocation testing, and skin test−negative iobitridol was given and tolerated during a mandatory radiological examination. Four patients rejected provocation testing.

DISCUSSION

In accordance with previous publications, our data demonstrate that nonallergic RCM hypersensitivity is a common cause of mild anaphylactic reactions presenting as a pruritic flush, urticaria, and/or angioedema but without any significant cardiovascular or respiratory symptoms.[1-3,9] In those patients, diagnostic skin testing is uniformly negative. The pathogenesis of nonallergic RCM hypersensitivity is still unsolved. Direct histamine-liberating effects of RCM and nonspecific complement activation have been discussed.[21] Nonallergic hypersensitivity reactions are commonly attenuated if lower RCM doses are given or injection rates are reduced. Premedication with H_1 antihistamines and glucocorticoids may even completely suppress clinical symptoms.[13,17,18]

In contrast, there is growing evidence that severe anaphylaxis is caused by immediate-type RCM allergy.[3,5,9] These reactions are most likely IgE-mediated, even if there is only indirect evidence of RCM-directed IgE antibodies as indicated by positive results of intradermal and basophil activation testing.[3,5] IgE antibodies to individual ionic RCM were detected in small quantities.[22,23] Attempts to demonstrate specific IgE binding to modern nonionic RCM failed because of difficulties in linking the chemically inert RCM to a carrier.[5]

Delayed-type hypersensitivity reactions occur within hours to days after injection of iodinated RCM and usually present as MPE, which is probably caused by activated T cells.[5,24] Variants of nonimmediate drug reactions including flexural exanthem or

systemic hypersensitivity were occasionally described.[25,26] RCM, however, do not belong to the common causes of drug-induced hypersensitivity syndrome, also referred to as DRESS.[20,26] In our series, DRESS was diagnosed in 1 patient who developed a widespread and severe exanthem accompanied by significant hepatitis within a few days after injection of iomeprol. Our cohort additionally includes a fixed drug eruption following exposure to iobitridol. Intradermal testing of the culprit RCM was positive only within formerly affected skin areas, as is typical for this entity.[19]

To prevent false-positive test reactions, intradermal testing of iodinated RCM requires dilutions of at least 1:10, meaning that test concentrations should not exceed 10% of the concentration used for radiological diagnostics.[6] Because irritant reactions are strongly dose-dependent, any borderline wheal-and-flare reaction should be verified by additional testing of a 1:100 dilution.[27] Allergic test reactions are expected to persist or only slightly decrease upon further dilution, whereas irritant reactions are no longer detectable.

The sensitivity of skin testing with iodinated RCM for the detection of immediate- or delayed-type RCM is commonly reported to be high, which was explained by the fact that RCM are not subject to any biotransformation.[28,29] Previously published sensitivity rates, however, considerably differ, ranging from less than 50% to more than 90%.[7-11] The sensitivity of intradermal testing both *in general* and in the diagnostics of RCM allergy obviously depends on accurate execution and experience of the examiner.[6,27] A late test reaction, for example, may be missed if readings are not performed on at least 2 or better 3 consecutive days. Moreover, the injection-induced bleb correlates with the injected volume and should measure 3 to 5 mm.[6] The sensitivity of intradermal testing may be impaired if the injected volume is too small. The manufacturer guarantees stable concentrations of iodinated RCM in unopened packages before the expiration date. Understandably enough, there are no available data regarding the stability of 1:10 RCM solutions for allergy testing. It is quite possible that the absolute quantity of the active ingredient does not remain stable upon dilution and may decrease as a result of physicochemical reactions and/or interaction with the material of syringes.[30] Consequently, diluted RCM solutions should be prepared immediately before testing and used within 1 hour. Before each injection, the solution within the syringe ought to be checked for signs of precipitation or inhomogeneity to be replaced if necessary.

Several groups reported on the detection of RCM-specific sensitization by cellular tests, that is, basophil activation or lymphocyte transformation.[3,24] These methods, however, are available only in specialized laboratories and cannot be recommended for routine diagnostic use.

Controlled provocation testing of skin test−negative RCM was proposed as final proof of tolerance.[2,5] However, a recent international consensus document dealing with controversial issues of RCM hypersensitivity noticed that there is no generally accepted standard for provocation testing.[31] As specified above, total doses of approximately 50 mL RCM solution were administered within 2 to 3 hours in our cohort. In other studies, varying amounts of iodinated RCM (10-100 mL) were injected on a single day or incrementally increased over several days.[7,8,32,33] In comparison, 100 to 150 mL of an RCM solution with iodine strength of 300 mg/mL is estimated for full-body computed tomography and 1 to 1.5 mL/kg body weight for urography. The dose of the provocation test in our study is thus within the lower limit of a usual dose used for an X-ray procedure. Moreover, because the minimum amount of an allergen required to induce a clinically apparent reaction supposedly ranges between low and even very low dose levels, a dose of approximately 50 mL should reliably trigger a reaction in an individual sensitized to RCM.[34] In our series, provocation with skin test−negative RCM was invariably tolerated, which confirms the excellent sensitivity of intradermal testing in patients with RCM allergy.

Previous studies assessing RCM-induced hypersensitivity considerably differ with regard to the substance panels included for testing and the most commonly identified causes of RCM allergy.[7-11] These differences presumably reflect regional standards regarding the choice of RCM for radiological diagnostics. Immunologic cross-reactivity between RCM is commonly observed, and reported proportions of patients with cross-reactions range from 20% up to 75%.[6-10] In our cohort of 22 patients with RCM allergy, sensitization to only 1 RCM was detected in 11 patients, 6 of whom, however, were tested with only 3 different RCM. No uniform or reproducible pattern of cross-reactivity between individual RCM can be deduced from the available literature, and structural formulas of individual RCM do not permit one to predict immunologic cross-reactivity. Iodinated RCM are monomeric or dimeric derivatives of triiodobenzoic acid, with different organic side chains attached to the central benzene ring. Chemical structures of these side chains, however, are very similar, and any 2-dimensional formula can only imperfectly depict the complex 3-dimensional conformation recognized by an IgE antibody. There is some evidence that iobitridol has a comparatively low tendency to cross-react with other RCM.[7,8,11,35] Of the total 16 patients sensitized to iomeprol in our study group, only 2 were cosensitized to iopamidol. This observation stands in some contrast to the recent study by Lerondeau et al[32] assigning both iomeprol and iopamidol into one subgroup of potentially cross-reactive RCM.[32]

The iodine molecule effectively absorbs X-rays, but is too toxic for diagnostic use in its inorganic form. In currently used RCM, it is covalently bound to the central benzene ring, resulting in a calculated iodine concentration of 150 to 350 mg/mL.[29] RCM solutions contain small quantities of free iodide (up to 50 μg/mL immediately after production), which tend to increase during shelf-life due to deiodization of the benzene ring.[36] The RCM molecule is subject to further deiodization in the human body. The resulting iodide load by far exceeds the recommended daily intake of 150 to 200 μg and may trigger incident hyperthyroidism.[16,37] Iodine allergy as cause of RCM hypersensitivity is nonetheless considered to be exceedingly rare and has even been referred to as "iodine allergy myth."[13,38] Our current series and previous reports, however, demonstrate that RCM-induced MPE may occasionally be triggered by free iodine or iodide rather than by the RCM molecule itself.[12] Our 2 patients reliably tolerated iodine-rich foods including seafood and iodized salt as well as topical application of povidone iodine−based antiseptics. Edible seaweeds such as kelp or *wakame*, which are commonly consumed in Japan and contain extreme amounts of iodide, may nonetheless cause exanthematous skin reactions in sensitized individuals.[39] These observations suggest that the clinical response depends on the iodine dose, way of contact, and possibly the redox state of iodine. Standard doses of any (though skin test−negative) RCM are very likely to provoke recurring MPE in these iodine-sensitive patients.

CONCLUSIONS

1. Anaphylaxis-like reactions occurring within minutes after injection of iodinated RCM may result from either nonallergic hypersensitivity or presumed genuine IgE-mediated allergy.
2. Nonallergic hypersensitivity reactions are generally mild, with symptoms remaining confined to the skin, and premedication is recommended to prevent future reactions. IgE-mediated RCM allergy, however, causes moderate to severe anaphylaxis with considerable respiratory, cardiovascular, and gastrointestinal involvement.
3. Nonimmediate RCM hypersensitivity commonly causes MPE with an onset hours to days after exposure and may occasionally trigger other variants of drug reactions including flexural exanthem, fixed drug eruption, or systemic hypersensitivity syndrome (DRESS).
4. Intradermal testing of RCM at dilutions of 1:10 may be an appropriate method for the diagnosis of RCM allergy.
5. Intravenous provocation with a skin test—negative RCM as final proof of tolerance appears safe in both delayed- and immediate-type RCM allergy and may someday become the gold standard of testing.
6. Iodine allergy is an occasional and possibly underdiagnosed cause of RCM-induced MPE and cannot be detected by intradermal testing of RCM. Additional prick, patch, and open application testing of iodine tincture is required for the detection of iodine allergy.

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