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Hypersensitivity reactions and contrast medium injection: Are they always related?

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ABSTRACT

Background: Hypersensitivity (allergic or non-allergic) reactions that occur after contrast medium (CM) injection are usually related to the CM. Recent studies, and case reports lack the analysis of alternate causes that could be also responsible in individual cases.

Patients and methods: We investigated the individual relevant factor/causative agent of adult patients with hypersensitivity reactions that occurred in radiological units during CM-enhanced procedures (CT, angiography, urography, or MR-examinations). Both immediate and non-immediate (delayed) reactions were included. To find out the relevant agent a detailed patients' history was carefully analyzed. In addition, the records were retrospectively reviewed, and if indicated and possible laboratory (e.g. basophil activation test) and skin tests (e.g. prick) and/or provocations with CM-injections under routine conditions were performed.

Results: 38 patients (men $n = 21$) suspected for CM-hypersensitivity reactions were identified. These reactions were in most cases mild ($n = 21$), moderate reactions occurred in 13 cases, and four patients had severe reactions. In 28 patients the reactions were induced by the CM (iodinated CM in 25 cases). Four patients had reactions that were not CM-related (latex allergy, adenosine reaction, vasovagal reaction, unknown cause) and in six cases the reaction was partly CM-related (immunological activation was present due to the patients' diseases).

Conclusion: Our data support the hypothesis that in CM-enhanced procedures not only contrast materials but also a broad range of other factors may also induce hypersensitivity reactions. Therefore, the number of CM-induced hypersensitivity is smaller than initially suspected. The knowledge of the cause of a reaction is essential to effectively prevent its recurrence and to improve safety aspects in patients undergoing CM-injection. Larger trials should be performed to more specifically assess alternate causes in patients who acquire hypersensitivity reactions in CM-enhanced diagnostic procedures.

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1. Introduction

The majority of patients tolerated contrast media (CM) that are injected for contrast-enhanced diagnostic imaging procedures very well. Nevertheless, a remaining small proportion of patients acquires adverse reactions. Approximately 3–10% of patients receiving low-osmolar non-ionic iodinated CM exhibit reactions, and in 0.04% of the cases these reactions are severe [1,2].

Usually, all reactions that occur in patients after CM-application are related to the CM. In most cases this assumption would be true, but in some individual cases other factors could be also responsible for such reactions but unfortunately these factors are rarely discussed [3,4]. Since unknown factors/conditions could be harm-

ful for the patient, the causality of an adverse reaction should be clarified. Currently, to the best of our knowledge no paper exists that carefully analyzes the causes of hypersensitivity reaction in patients who underwent CM-application. Therefore, we evaluated the individual cause in patients with hypersensitivity reactions that occurred in the context of CM-enhanced examinations.

2. Patients and methods

Adult patients with a history of CM-hypersensitivity reactions were included in the investigation. Hypersensitivity reactions are defined as allergic or non-allergic (formerly called allergy-like) reactions that manifest with clinical features such as urticaria, angioedema, tachycardia, bronchospasm, hypotension and loss of consciousness (Table 1). Hypersensitivity reactions were further classified as either immediate (onset within 1 h after CM-application) or non-immediate/delayed (onset later than 1 h

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Table 1
Clinical features and severity grading of anaphylaxis.

Grade	Clinical features
Mild	Nausea, vomiting, flushing, mild urticaria or other anatomical limited skin disease (e.g. fixed drug eruption), itching → clinical features are selflimiting, no treatment is necessary
Moderate	Facial edema, angioedema, generalized urticaria or other skin disease (e.g. maculopapular exanthema), brochospasm, dyspnea, stridor, wheeze, moderate hypotension, tachycardia, chest or throat tightness, dizziness → treatment is required in radiology department, but the patient can be discharged following the examination
Severe	prolonged hypotension, angina, ventricular fibrillation, cardiac arrest, severe brochospasm, respiratory arrest, pulmonary edema, confusion, cardiovascular collapse, loss of consciousness, convulsion → reactions require hospitalization (in special units) for treatment

Modified after [26,27].

after CM-administration). Manifestations of non-immediate reactions such as fixed drug eruption and maculopapular exanthema were also included. The clinical features of the reactions were documented. Patients who reported only on heat feeling or other discomfort were excluded. The severity of the hypersensitivity was graded as mentioned in Table 1.

The analysis covered all procedures that need CM-injection (i.e. urography, angiography, CT- and MR-examinations). Previously, three patients have been published elsewhere [5–7].

The records were retrospectively analyzed, and if possible the patients' history was carefully and detailed (see Table 2) evaluated with respect of all possible causative agents.

Skin prick tests (SPT) were performed as described previously [8] with the following iodinated or Gd-containing CM: iodoxanol, ioxaglate-meglumine, iopamidol, amidotrizoate, ioxithalamate-meglumine, iohexol, iopentol, iomeprol, ioversol, iopromide, iobitridol and iotrolan. SPT were done if (1) indicated and (2) the patient gave her/his informed written consent.

We did not use previously published challenge protocol [9], because the injection of small volumes of CM (1) does not reflect the challenge under routine conditions, (2) bears the risk of false positive reactions (e.g. in anxious patients), and finally (3) might probably boost a reaction. If clinically indicated we challenged the

Table 2
Recommended questions for patients suspected for a CM-hypersensitivity.

1. Sequence of events: when did you recognise the first symptoms? After or even before CM-injection?
2. Boosting disease: do you actually suffer from one or more of the following diseases? Allergic bronchial asthma (time point of the last acute event? Which allergens are relevant?) Pollinosis (hey fever) (time point of the last acute event? Which allergens are relevant?) Histaminosis? Histamine releasing food? Histamine rich food ingestion? Histamine digestion problems? Coronary heart disease? Common cold disease? Infectious or non-infectious inflammatory disorder?
3. CM-independent reactions: are you afraid of injections or other diagnostic devices? Do you have hypotension problems? Do you have allergic reactions against latex, anaesthetics, heparin, and/or others drugs? Which drugs/devices have been used during the last CM-enhanced procedure?
4. Challenge under routine conditions: did you receive CM-injection after the reaction? Do you know the name of the given CM (ask the radiologist and/or analyze the patients' record)? What happened?

Table 3
Analysis of causative agents/factors in patients undergoing CM-enhanced radiological examination.

Number of patients	38
Men:women	21:17
Mean age (range) in years	50.2 (23–74)
CM application route	
Intravenous	36
Intraarterial	2
Premedication	3
Culprit CM	
Iopromide	20
Gadopentetate dimeglumine	7
Iotrolan	3
Iohexol	1
Iosimenol	1
Iomeprol	1
Unknown iodinated CM	5
Immediate reactions	30 ^a
Grade 1	14
Grade 2	12 ^a
Grade 3	4
Non-immediate (delayed) reactions	9 ^a
Grade 1	7
Grade 2	2 ^a
Grade 3	0
Reactions induced by CM	28
Iodinated non-ionic	25
Gd-DTPA	3
Reactions partly induced by CM	6
Iodinated non-ionic	4
Gd-DTPA	2
Reactions not induced by CM	4
Vaso-vagal reaction	1
Latex allergy	1
Adenosine	1
Unknown cause	1

^a One patient had both immediate and non-immediate reactions.

patients under clinical routine conditions and used normal CM-doses as mentioned previously [5,7].

BAT was done as described previously [10]. Briefly, basophil degranulation was measured flow cytometrically by using the BASOTEST® (ORPEGEN Pharma, Heidelberg, Germany) according to the manufacturers' instructions. 100 µl heparinized blood per test was mixed with the selected CM or with the oligopeptide formyl-Met-Leu-Phe (fMLP) as positive control, or the buffer as negative control, and incubated for 30 min at 37 °C (water bath). The reaction was stopped by a transfer of the tubes on ice for 5 min. The cells were stained with 20 µl staining solution containing both anti-CD63 (gp53) FITC (clone CLB-gran/12), and anti-IgE PE (clone G7-26) for 20 min on ice in the dark. Afterwards the erythrocytes were lysed and leukocytes were simultaneously fixed by adding FACS lysing solution (Becton-Dickinson [BD]). The cells were analyzed flow cytometrically by using a FACScan™ (BD) equipped with a 488 nm argon-laser and CellQuest™ software.

Data were expressed as mean ± standard deviation (SD). The normal distribution of the investigated subsets was checked by the Kolmogorov–Smirnov test. Significance of differences between means was calculated using the Student's *t*-test (normal distributed data), and the Wilcoxon or the Mann–Whitney *U*-test has been used for non-normal distributed data. Differences between values were considered statistically significant at *p* < 0.05.

3. Results

We identified 38 patients who met the above mentioned inclusion criteria. Table 3 summarizes the data from 38 investigated patients. They had a mean age 50.2 years (±13.7 years). 21 (mean age 51.7 years ± 13.6 years) were men, and 17 (mean age 48.5 years ± 14.1 years) women.

Table 4

Clinical features of 38 patients suspected for CM-induced reactions and its absolute frequency.

Symptoms	Frequency
Dyspnea/bronchospasmus	16
Hypoxia	2
Hypotension	5
Loss of consciousness	1
Itching	9
Urticaria	23
Angioedema	5
Respiratory arrest	2
Erythema/flushing	11
Nausea/vomiting	5
Heat/cold feeling ^a	13
Tachycardia	4
Maculo-papular exanthema	2
Arthralgia	1
Headache	1
Dizziness	1
Fixed drug eruption	1
Cardiac arrest	1

^a No single or isolated symptom.

Most patients underwent CT examination ($n=28$), seven received MR scans, two patients underwent angiography, and one patient intravenous urography.

Most hypersensitivity reactions were mild ($n=21$), moderate reactions could be documented in 13 cases, and the remaining four had severe reactions. The patients with severe reactions (31.7 ± 7.1 years) were significantly ($p < 0.05$) younger than those with mild (51.0 ± 12.3 years) or moderate reactions (53.2 ± 13.3 years). The clinical features of these reactions are listed in Table 4.

Immediate reactions occurred in 30 patients, and nine patients had non-immediate (delayed) reactions. One patient had both an immediate reaction with bronchospasm, followed by a non-immediate reaction 24 h later with maculo-papular exanthema (for detailed information see [6]). Non-immediate reactions were mainly observed in patients who underwent CM-enhanced CT ($n=7$). Only one patient reported delayed (approximately 8 h after CM-injection) reactivity after Gd-DTPA-enhanced MR-examination.

Patients with immediate reactions were significantly younger than those with non-immediate reactions (47.9 ± 14.1 years versus 58.9 ± 8.4 ; $p < 0.05$).

CM as cause for the hypersensitivity could be detected in 28 patients (men $n=15$, women $n=13$). The patients had a mean age of 50.5 years (± 14.3 years). Iodinated non-ionic CM was responsible for the reactions in 25 cases, and Gd-containing CM for the remaining three patients. 22 (78.6%) CM-induced reactions were immediate, and 6 (21.4%) non-immediate. Mild reactions occurred in 19 patients, moderate reactions in 7 patients, and two patients had severe reactions.

In six patients (men $n=2$) with a mean age of 47.5 years (± 9.4 years) the hypersensitivity reactions were partly induced by contrast materials, and partly by a special immunological condition (see Table 3). These reactions occurred in five patients immediately, only one patient had a delayed reaction. Mild reactions could be documented in two patients, three had moderate reactions, and one patient showed a severe reactivity. Four patients underwent CM-enhanced CT, and two patients MR-examinations.

We found four patients with non-CM causes (i.e. vasovagal reaction, latex allergy, adenosine reaction, and an unknown cause). They were all men, and had a mean age of 52.8 years (± 18.1 years). Three patients had immediate reactions, and in one case the reaction occurred delayed. Mild reactions could not be observed. Three patients had moderate reactions, and in one case the reaction was

severe. Two patients underwent CM-enhanced MR-examination, one patient CT, and one angiography.

CM could be excluded as responsible agent, because

- the reaction could be induced by a venous punctation in a 29-year old man (after successful treatment and a concrete question he told the physician that he is afraid of injection needles. Formerly, he did not mention this fact because he was ashamed of this);
- the reaction occurred before iodinated CM-injection, the patient had intense contact to latex-containing devices, and afterwards an allergological work-out showed a latex allergy;
- the reaction was only present when the patient received both adenosine and gadopentetate dimeglumine (Magnevist®);
- some months after the delayed reaction that was initially suspected as Gd-CM-induced reaction, the patient again received Gd-DTPA and tolerated it very well without premedication.

11/38 (28.9%) patients (men $n=6$) were challenged with either iodinated non-ionic CM ($n=9$) or with Gd-DTPA ($n=2$). Of these 11 patients the reaction was mild in four cases, and moderate in seven cases. The same contrast agent that initially induced the reaction was used in seven patients, and five patients received other CM (i.e. iodinated CM instead of Gd-CM or another iodinated CM). One patient received both initially the same CM, and then another. In patients who received the same CM again, four reacted again, and three did not react.

One 32-year-old male patient who showed a severe reaction (dyspnea, and cardiovascular collapse with subsequent emergency treatment in special unit) after non-ionic iodinated CM-injection for CM-enhanced CT never received CM-administration again.

In 26 patients there was no information available as to whether a challenge with CM was done or not.

4. Discussion

This paper for the first time shows the great clinical impact to critically reflect the individual cause of hypersensitivity reactions that occur in the concert with CM-injections. Primarily, the search for alternate causative factors in patients who received CM-injection seems to be nonsense. But a closer look shows that in addition to both major groups of contrast materials – iodinated and gadolinium-containing CM – a variety of other factors could also be responsible in individual cases who acquired hypersensitivity reactions in radiological units/clinics. Especially patients who undergo CM-enhanced interventional procedures have contact to several other drugs (e.g. anaesthetics, heparin) and materials that could also cause adverse events as shown above. Therefore, it is surprisingly that adverse reactions that occur in patients who received CM-injection, are solely related to the contrast materials, and all other potential causes are neglected. Interestingly, this is not only true for hypersensitivity reactions but also for graft-versus-host disease [11]. It could be likely that former experiences with ionic CM of high osmolality that induced in a great proportion of patients adverse events still influences such relations. Another point could be that in routine practice is not time enough to critically reflect other causes.

We could show that a subtle work-out revealed several alternate causes including vaso-vagal reaction, latex allergy, adverse adenosine reactivity, and an unknown factor (Table 3). Although these causes are theoretically known [3,4,12–16], practically this knowledge seems to play no role in every-day routine, and even studies dealing with safety aspects and frequencies of adverse CM-reactions do not mention possible alternate causes of unwanted events [8,9,17].

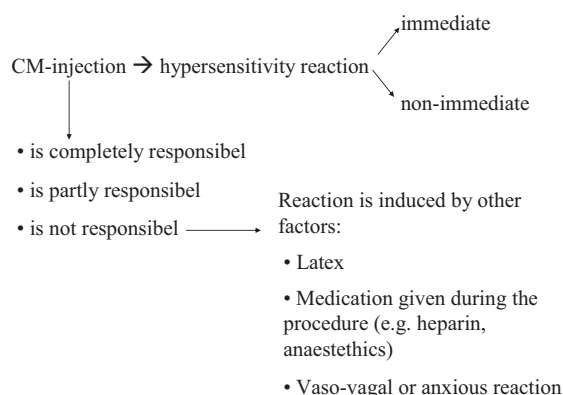


Fig. 1. Schematic drawing showing flow chart of CM-injection and related hypersensitivity reactions including three possible causative connections.

The herein presented data show that if a hypersensitivity reaction occurs after CM-application, there are at least three causal possibilities (see Fig. 1): (1) the CM has caused the reaction, (2) the CM has not caused the reaction, and (3) the reaction depends only partly on the CM-injection. The first point summarizes conditions in which the CM is responsible for the reaction (in rare cases simultaneous hypersensitivity reactions exist against both CM and another drug [18]). Therefore, the risk for a relapse is increased after CM re-exposure as shown in four cases who were challenged with the same CM that initially induced the reaction, and who reacted again (see Results under Challenge). Avoidance of CM-application is the best prophylactic strategy. One should realize that the use of other chemical CM types (e.g. gadolinium-containing CM instead of iodinated CM or vice versa) does not necessarily prevent a relapse, because patients may react to both Gd-CM and iodinated CM [5,7]. If CM-injection could not be omitted an allergological work-out should reveal tolerated and non-tolerated contrast agents [7,8]. Herein four of five patients who received an alternate CM after the initial hypersensitivity reaction were tested. Afterwards they were re-exposed to a negatively skin-tested CM, and tolerated this CM-application very well. Premedication with glucocorticosteroids and/or antihistaminics (H1- and H2-blockers) is another possibility to improve the tolerability. But one should realize that premedication does not completely prevent hypersensitivity reactions [7,19]. Moreover, corticosteroids used as premedication may themselves induce an allergic reaction [18].

CM is the responsible agent for individual hypersensitivity reactions when other factors (see below) could be excluded. SPT is an important diagnostic tool but a negative test result does not exclude CM as responsible agent. Therefore, in addition to the SPT the patients' history should be also taken into account.

The second situation means that other factors may have induced the adverse event. Possible alternate causes comprises of a broad spectrum of factors such as vasovagal or anxious induced reaction, latex, and/or medication used during CM-enhanced procedure (e.g. anaesthetics, heparin, colloid plasma expander, adenosine (Table 3), physiological saline solution) [3,12–16,20,21]. A detailed history and – if possible – an allergological work-out should help to find causative factor(s), and to effectively manage the secondary prophylaxis. In individual cases an interdisciplinary management could be necessary to efficiently avoid the recurrence of a reaction. Moreover, the patients' history before the patient undergoes CM-injection should be carefully done to possibly detect special conditions (see above) that could increase the risk for an adverse reaction. Furthermore, studies dealing with safety aspects of iodinated or Gd-containing CM should not only present frequencies of adverse reactions, but should also critically reflect other causative agents.

Now it is unclear why skin testing (prick, intracutaneous) is negative in many cases [8,9,22]. One explanation could be that CM induces only in a small proportion of patients an allergy [9]. Another explanation could be that individuals with negative skin test did not reacted to the CM. There are several reasons for negative SPT results: (1) CM is not the cause of the reaction (causative incompatibility), (2) the reaction depends only partly on the CM, and is no longer present when the patient is tested (partial causative incompatibility); (3) CM is responsible for the reaction, but SPT is not the suitable test modality (e.g. in patients with fixed drug eruption or the patient has a low grade allergy which does not allow testing (test incompatibility) [22]; (4) false negative test results due to wrong CM selection which does not include the culprit CM, CM concentration is too low, the patient is not testable because he/she is under anti-allergic medication or UV skin exposition inhibits a positive result (test procedure incompatibility).

The third condition shows that the CM may be responsible for a hypersensitivity reaction under special circumstances like intense stimulation of the immune system (see Table 3). This fact has been rarely mentioned. Previously, it has been shown that iodinated contrast media alter immune responses in pro-inflammatory states [23]. Moreover, recently it has been pointed out that asthma per se does not increase the risk for a CM-hypersensitivity [24,25]. Severe hypersensitivity reactions shortly before the patient received CM-injection, and all other immunological stimulations (e.g. sepsis) should be documented. Moreover, in elective CM-enhanced examinations it would be useful to wait until an acute inflammatory reaction has cleared.

Taken together the paper shows that careful analysis of the causality is of great clinical impact in CM suspected adverse events. The CM could be responsible for a reaction, but alternate factors should be also taken into account. If hypersensitivity reactions occur after CM-injection it is recommended to carefully exclude other possible factors as shown above. Especially, in interventional radiological procedures when multiple drugs are used a thorough analysis of the causative agent is necessary to prevent adverse reactions in future procedures. Knowledge about the causative agent helps to further improve the personalized management of patients with reactions during CM-enhanced procedures.

Conflict of interest

There is no conflict of interest.

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