Immediate and Delayed Cutaneous Reactions to Radiocontrast Media

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Abstract
Hypersensitivity reactions to contrast media (CM) are frequent causes of anaphylaxis and drug exanthemas. Adverse events after CM exposure are classified into immediate (≤1 h) and non-immediate reactions (>1 h), with differing mechanisms. In the majority of patients with immediate reactions, IgE-mediated allergy cannot be demonstrated, and the underlying mechanism remains unknown. However, recent data have provided evidence for skin test positivity and/or specific IgE in some patients. T cell-mediated hypersensitivity is the responsible mechanism for the majority of non-immediate skin eruptions. These insights have consequences for diagnosis and prevention. Skin testing evolves to be a useful tool for diagnosis of CM allergy. Skin tests have been employed to confirm this hypersensitivity. Previous reactors have an increased risk to develop new reactions upon repeated exposure; however, other risk factors are poorly defined. The use of skin tests for the selection of a ‘safe’ CM is under investigation with promising results. In vitro tests to search for CM-specific cell activation include flow cytometric approaches, lymphocyte cultures and construction of cell lines and hybridomas. Premedication of previous reactors is common practice among radiologists; however, breakthrough reactions are a concern, and physicians should not rely on the efficacy of pharmacological premedication.

Essentials in a Nutshell

- Modern radiocontrast media (RCM) lead to hypersensitivity reactions in 1–3% of applications
- Adverse reactions to RCM may be classified into toxic, unrelated/unspecific and immediate or non-immediate hypersensitivity reactions
- The manifestation of immediate hypersensitivity reactions is anaphylaxis
- Exanthemas are the predominant clinical picture of non-immediate RCM hypersensitivity and resemble those to other drugs
- There is growing evidence that the mechanism of immediate hypersensitivity to RCM may be IgE mediated, and that of non-immediate skin eruptions is T cell mediated. Allergy to iodine does not play a major role
• Skin tests are of value as a screening test for allergy to RCM hypersensitivity, and may be used to select a radiographic contrast medium (CM) for future use.
• Provocation tests are recommended to validate skin tests in non-immediate exanthemas.
• As prevention, a different skin test-negative RCM should be chosen for future examinations. Doctors should not rely on the efficacy of premedication.

**Epidemiology of Hypersensitivity Reactions to Radiocontrast Media**

RCM are concentrated solutions of tri-iodinated benzene derivatives. Non-ionic monomers are most commonly used, whereas the older ionic monomers are not available any more in many countries, and only one non-ionic dimeric preparation is available for intravenous use. RCM are used for the diagnosis and treatment of vascular disease and enhancement of radiographic contrast [1]. Adverse reactions after application of RCM are common [2]. The frequency hypersensitivity reactions differs between different types of RCM. Mild immediate reactions, such as urticaria and pruritus have been reported to occur in up to 12.7% of patients receiving the older ionic monomeric RCM, but only in 0.7–3.1% of patients receiving the modern non-ionic RCM [3]. Severe immediate adverse reactions to ionic RCM have been reported in 0.1–0.4% of procedures, but only in 0.02–0.04% of applications of nowadays non-ionic RCM [reviewed in 4]. Fatal hypersensitivity reactions still occur in 1–3 per 100,000 CM administrations to both ionic and non-ionic preparations. The frequency of reported non-immediate reactions varies greatly between publications. Skin exanthemas (skin rash, skin eruptions) account for the majority of the RCM-induced non-immediate hypersensitivity reactions, and can be estimated to affect 1–3% of RCM-exposed patients [5]. There appears to be a higher incidence of exanthemas associated with dimeric non-ionic RCM. The only well-established risk factor for immediate as well as non-immediate hypersensitivity reactions are a previous hypersensitivity reaction [5, 6]. It is of interest that immediate reactions are not risk factors for developing a non-immediate reaction and vice versa.

**Classification of Radiographic Contrast Media Hypersensitivity Reactions**

Not all symptoms after RCM exposure resemble real hypersensitivity reactions (fig. 1). Toxic reactions to RCM are well known, e.g. nephrotoxicity or neurotoxicity. The unspecific feeling of warmth should also not be confused with a real hypersensitivity reaction. Unspecific reactions of unknown origin and or unrelated diseases may also occur after application of RCM, such as unrelated chronic idiopathic...
urticaria [2]. In a recent study on 539 patients receiving either computed tomography unenhanced or enhanced with iohexol, also 2.5% of 281 with no CM application reported reactions [7]. Typical hypersensitivity reactions to RCM may either present under the clinical picture of anaphylaxis, or as delayed occurring exanthema. In an attempt for classification, they have been differentiated with regard to the time interval between administration and the first appearance of symptoms as immediate, when they occur within 1 h after RCM administration, or non-immediate, when they occur 1 h up to 10 days after RCM application [2]. The present review will give an update on our present understanding of immediate and non-immediate hypersensitivity reactions to RCM.

**Clinical Presentations of Immediate and Non-Immediate Hypersensitivity**

Immediate RCM hypersensitivity reactions manifest as anaphylaxis (table 1). The majority of patients with immediate reaction present with pruritus and urticaria; sometimes angioedema occurs [4]. For several other frequent reactions, such as nausea, and vomiting, however, it remains unclear, if these reactions represent hypersensitivity or rather toxic reactions. Gastrointestinal symptoms such as

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**Fig. 1.** Classification of adverse reactions to RCM. Adapted from Brockow et al. [2].
abdominal pain and diarrhea may occur. More severe reactions involve the respiratory and cardiovascular systems and present with dyspnea, bronchospasm, and/or a sudden drop in blood pressure. Hypotension is mostly combined with reflex tachycardia and can be associated with a loss of consciousness (anaphylactic shock) [2]. About 70% of those reactions occur within 5 min after injection [8], and 96% of severe or fatal reactions manifest within 20 min [4]. The grading system published by Ring and Messmer is helpful for scoring the severity of anaphylaxis regardless of the mechanism [9].

Most patients with a non-immediate RCM reaction present with a macular or maculopapular exanthema (fig. 2a). It may occur only some hours, but also several days after the RCM administration (table 1) [5, 8]. More specific exanthemas after RCM exposure include symmetrical drug-related intertriginous and flexural exanthema (SDRIFE; fig. 2b), or drug-related eosinophilia with systemic symptoms (DRESS). Other skin reactions have been described, such as fixed drug eruption, erythema exsudativum multiforme, scaling skin eruption, graft-versus-host reaction, pruritus and pompholyx [1, 4]. Most non-immediate RCM hypersensitivity reactions are mild to moderate in severity and are self-limited [8]. Some rare cases of severe reactions have also been reported, presenting with cutaneous vasculitis, DRESS syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis and papulopustular eruptions [2]. Sometimes mild non-immediate anaphylactoid symptoms are reported, such as erythema, urticaria, or angioedema occurring hours after RCM application. Most of these may be regarded as exanthemas, such as the facial angioedema typical for DRESS syndrome. Systemic symptoms with delayed more anaphylactoid manifestations such as hypotension, fever, abdominal pain, dyspnea after several hours and biphasic reactions had been reported when dimeric non-ionic RCM had been introduced. However, even in dimeric non-ionic RCM they do appear to be very uncommon [2].

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<tr>
<th>Table 1. Clinical pictures of typical immediate and non-immediate hypersensitivity reactions to RCM</th>
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<tr>
<td>Anaphylactic immediate reactions</td>
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<tr>
<td>Urticaria</td>
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<tr>
<td>Angioedema/facial edema</td>
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<tr>
<td>Abdominal pain, nausea, or diarrhea</td>
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<td>Rhinitis (sneezing, rhinorrhea)</td>
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<td>Hoarseness, cough</td>
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<tr>
<td>Dyspnea (bronchospasm, laryngeal edema)</td>
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<td>Respiratory arrest</td>
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<td>Hypotension, cardiovascular shock</td>
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<td>Cardiac arrest</td>
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Immediate Radiocontrast Media Hypersensitivity

The mechanisms of the allergy-like reactions to RCM are still under investigation [4]. Anaphylaxis to RCM has been discussed to be due either to a direct membrane effect related to the osmolality of the CM or the chemical structure of the CM molecule (pseudoallergy), complement activation, bradykinin formation, or an IgE-mediated mechanism [4].

There is some indirect evidence that immediate hypersensitivity reactions may be caused by an IgE-mediated allergic mechanism. First, immediate hypersensitivity reactions to CM are associated with histamine release from basophils and mast cells, and extensive mast cell activation in vivo associated with clinical symptoms has been demonstrated by Laroche et al. [10]. Patients with hypersensitivity reactions after CM exposure had increased plasma levels of both histamine and tryptase, and levels correlated with severity [10, 11].

Second, several groups have reported positive skin test results for patients with severe immediate reactions to either ionic or non-ionic RCM [8]. Some of these
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Patients were shown to react not only to the skin test of the culprit CM but also to other CM [8]. The frequency of positive skin tests has been investigated in a European multicenter study in patients with RCM hypersensitivity and in 82 controls [8]. The intradermal test (IDT) showed specificity in 96.3% of controls, but was positive in only 26% of patients. Another recent French prospective clinical study on 38 patients with immediate hypersensitivity reactions to RCM as determined by a reaction at the Radiology Department examined clinical data, serum and plasma analysis of tryptase and histamine as well as skin test reactivity to RCM [12]. In this study employing higher (undiluted) RCM concentrations, positive skin test reactions were even found in 73% of patients. Patients with more severe reactions had more positive skin test reactions and higher plasma histamine and tryptase levels after the reaction. Cross-reactivity between different RCM was rare, supporting the non-irritative character of the skin tests; however, control patients as a proof of specificity of the reactions were missing.

In vitro, positive basophil activation tests were reported in patients with immediate RCM hypersensitivity reactions, which may be regarded as another indirect indication for an IgE-mediated allergy [13]. Older studies also demonstrated CM-specific IgE by immunoassays [reviewed in 4]. Unfortunately, these results have not been confirmed by newer studies and/or for the modern non-ionic RCM, as it is difficult to bind non-ionic RCM to a solid phase, limiting research in this field.

Pathophysiology of Non-Immediate Reactions

The majority of these reactions appear to be T cell-mediated reactions. First, the most common clinical picture of non-immediate RCM reactions is a maculopapular exanthema, which resembles other drug-induced allergic T cell-mediated hypersensitivity reactions. The reported onset of skin eruptions 2–10 days after the first exposure to an RCM and 1–2 days after reexposure to the same substance is compatible with an allergic drug reaction and with a sensitization phase. Previous reactors are at risk for a new reaction compatible with a sensitization. In many cases, readministration of the culprit CM to patients with a previous non-immediate exanthema resulted in a repeat reaction [1].

Second, the histopathology of those exanthemas and of positive skin test sites provides evidence for an involvement of T cells [14, 15]. The perivascular infiltrate of positive skin test site biopsies consist mainly of CD4+ and CD8+ (CD45RO+) T cells accompanied by eosinophils [14, 15]. Also skin biopsies obtained from the site of positive skin tests to the culprit RCM showed similar results, with high expression of CD69 in lymphocytes [15–17].

Positive delayed skin tests in patients with CM-induced non-immediate skin reactions have been frequently reported [summarized in 1]. In a European multicenter study with 220 patients, 37% of patients with non-immediate reactions were positive.
in delayed IDTs and/or patch tests [8]. The majority of the patients reacted to the culprit CM and also to other CM indicating cross-reactivity.

The presence of RCM-specific T cells in patients with non-immediate exanthematous skin eruptions has been demonstrated in vitro in the lymphocyte transformation test [14], and by increased T lymphocyte activation markers (CD69, CD25 and HLA-D) by flow cytometric analysis, as well as by skin homing receptors (CLA) in CD4-positive lymphocytes. Perforin expression was increased in the CD8-positive cytotoxic lymphocytes [15]. When RCM-specific T cell clones were generated from human blood of three RCM-allergic patients and a specific T cell receptor was transfected into a mouse T cell hybridoma, RCM were stimulatory for T cells either by direct bridging of the major histocompatibility complex T cell receptor structure or by binding after uptake and processing by antigen-presenting cells [18]. This hapten-independent model would also better explain the cross-reactivity observed between different compounds, and challenges the assumed inert nature of RCM.

**Role of Iodine in Contrast Media Hypersensitivity**

In 19 patients with immediate or non-immediate RCM hypersensitivity reactions to RCM, skin tests with several RCM and iodine were done and oral provocation with Lugol’s solution was performed [19]. Out of 9 patients with immediate hypersensitivity, skin tests to RCM were positive in 3 (33%). Skin tests to iodine preparations remained negative, but one skin test-negative patient reacted twice to oral iodine with urticaria. All 10 patients (100%) with non-immediate reactions showed positive skin tests to RCM. Even though in 7/10 (70%) additional positive skin tests to the iodine formulations were found, only 2 patients (20%) with extensive cross-reactivity between RCM developed a mild exanthema after oral provocation with Lugol’s solution. This study confirmed that iodine is rarely the eliciting agent in RCM hypersensitivity.

**Diagnosis**

Immediately after the reaction, an RCM-induced anaphylaxis may be confirmed by blood samples for histamine analysis drawn as soon as possible after the reaction and/or by tryptase analysis of a sample drawn 1–2 h after onset of symptoms [10]. Tryptase values have to be compared to baseline levels and significant increases indicate anaphylaxis. In non-immediate reactions, hematology and clinical chemistry should be considered in more severe exanthema to exclude systemic involvement [1]. A skin biopsy may sometimes help in the differential diagnosis.

The further allergologic workup is recommended to be performed between 2 and 6 months after the reaction, as this is associated with a much higher frequency of positive skin test reactions as compared with longer time intervals (table 2) [8].
Skin Tests

A skin prick test (SPT) should be performed with undiluted RCM. As skin test reactions resemble the original reaction, for immediate reactions readings after 20 min are indicated, whereas for non-immediate reactions additional readings after 48 and 72 h have to be done. A positive reaction in the SPT is rare, but it is a good screening test for a strong sensitivity. Systemic reactions to IDT have been described. Afterwards, IDTs with RCM (300–320 mgI/ml) diluted 10-fold in sterile saline and reading after 20 min have been recommended [8]. IDTs with undiluted RCM had been reported in non-severe reactions to increase sensitivity; however, at the cost of an undetermined specificity [12]. As cross-reactivity is frequent, a panel of several different RCM should be tested in an attempt to find a skin test-negative product, which might be tolerated in future RCM examinations. Both delayed IDTs and patch tests are frequently positive, when read after 48 and 72 h, but the best time points for readings have not been compared, and in the case of local pruritus or erythematous plaques additional readings at other time points are advisable, e.g. 24, 96 h. Patch tests should be conducted with undiluted CM. Since rare patients tested positive with either IDT or patch test only, it is recommended to use both tests in parallel (table 2). In summary, skin tests are best screening tests to demonstrate an immunological mechanism in patients with RCM hypersensitivity. When used with the concentrations recommended, they have a high specificity and only a moderate sensitivity.

Laboratory Tests

In immediate RCM hypersensitivity, there is no assay for routine measurement of serum levels of RCM-specific IgE antibodies available. The reliability of other in
vitro tests, such as the basophil activation test has not yet been established. Highly increased CD63 expressions in patients with immediate hypersensitivity reactions in vitro indicate that the basophil activation test may be helpful in individual patients [13]. RCM-related T cell activity in non-immediate hypersensitivity may be assessed in vitro by lymphocyte transformation test [14, 15]. This, however, appears to have a lower sensitivity as compared to skin tests [own unpubl. obs.]. In addition, CD69 upregulation (lymphocyte activation test) was observed in patients with positive lymphocyte transformation tests [15]. These tests appear to be a promising tool to identify drug-reactive T cells in the peripheral blood of patients with RCM-induced drug hypersensitivity reactions. Further research on the specificity and sensitivity is indicated.

**Provocation Tests**

Whereas in immediate hypersensitivity provocation is not generally recommended, as intravenous applications of as low as 0.5–1 ml RCM have led to severe anaphylaxis, in non-severe non-immediate hypersensitivity, provocation tests can validate skin test results and are recommended. Until further results are available, a positive skin test to a given RCM dictates that this RCM should not be chosen for a future exposure as alone the epicutaneous or intradermal application was able to lead to a local reaction, but a negative test does not necessarily guarantee tolerance. Here, provocation tests are helpful, depending on the time course of the primary reaction: e.g. 1/10 of the full dose on day 1, 1/2 of this volume on day 2 and the full dose on day 3 at the Radiology Department [20]. Provocation tests should be performed only in centers with experience to perform monitoring and emergency treatment. Noteworthy, a previous non-immediate exanthematous reaction does not pose a higher risk for a subsequent immediate anaphylactic reaction. In one study, safe readministration of a skin test-negative CM has been published in a series of 15 patients with non-immediate skin eruptions [20]. In this study, however, non-serious skin symptoms after exposure to the dimeric agents iodixanol (n = 4) or ioxaglate (n = 1) were described despite negative skin tests for these agents. In contrast, in a more recent study, a negative predictive value of 96.6% was calculated, when skin tests had been negative [21]. Out of 159 patients who had been skin tested and advised to use a skin test-negative RCM for further procedures, 29 patients were identified who had been reexposed to RCM after they had experienced an immediate (n = 24) or non-immediate (n = 4) hypersensitivity reaction. Of those patients, only 2 reported mild reactions to the subsequent examination. Thus, skin tests are probably helpful in the selection of a tolerable RCM in a patient with previous hypersensitivity reaction, but preliminary results should be further validated in a European multicenter follow-up study by provocation tests and reexposure data.
Prevention

In patients with a previous immediate hypersensitivity reaction to an RCM, the culprit preparation should be avoided in a new contrasted examination because of growing evidence that the hypersensitivity reaction may be structure dependent. Skin tests (SPT and IDT) with RCM are recommended [1]. RCM with positive skin tests should be avoided because of cross-reactivity among RCM [8]. In those patients who develop no positive skin test reaction to the culprit or other RCM, a negative skin test does not guarantee tolerance. However, the overall risk of a repeat reaction was very low according to a recent study, indicating a high negative predictive value. The use of premedication in patients at high risk for immediate RCM reactions has recently been challenged [22]. Corticosteroids and H1 and H2 antihistamines are the most frequently used agents with different protocols and administration routes. However, severe reactions still may develop in patients who receive corticosteroid premedication and the recurrence rate of RCM reaction after corticosteroid administration has been estimated to be almost 10% in one study [23]. In a recent study in 30 patients who had been pretreated with corticosteroid and H₁ antihistamines and/or H₂ blockers, immediate hypersensitivity reactions were not prevented in 5 of 30 patients (17%) with prior RCM reactions with similar severity and clinical manifestations [24]. In unselected patients, the usefulness of premedication is doubtful [22]. Sufficient data supporting the use of premedication in patients with a history of allergic reactions only are lacking. In summary, physicians dealing with these patients should not rely on the efficacy of premedication [22].

Similarly, patients with previous non-immediate skin exanthemas to RCM are at risk for developing new eruptions upon reexposure to the RCM [1], and another RCM should be chosen if reexposure is required. Due to frequent cross-reactivity between different RCM, an unselected change of product is no guarantee against a repeat reaction. PT and delayed IDT are recommended [8]. In case of positive skin tests, the substances that are able to elicit test reactions should be avoided. At present, the administration of skin test-negative CM in previous reactors does not guarantee tolerability, but appears to be associated with high negative predictive value even without pretreatment. In non-severe hypersensitivity (e.g. not in blistering reactions, systemic symptoms), a fractionated provocation test is indicated. In current practice, steroid prophylaxis is given in patients with previous serious non-immediate adverse reactions with partial success. However, repeated non-immediate reactions, including a case of toxic epidermal necrolysis, have been reported despite corticosteroid pre-medication [25]. A more intensive immunosuppressant protocol used intramuscular 6-methyl-prednisolone (40 mg daily) and oral cyclosporine (100 mg twice daily) in a patient with two previous episodes of maculopapular reactions after RCM administration, the last despite steroid premedication [25]. No studies have been performed to establish the optimum pretreatment regimen.
References