M. B. Bilò[1,2], D. Bignardi[3]

Iodinated contrast media hypersensitivity reactions: is it time to re-evaluate risk factors?

[1]Department of Clinical and Molecular Sciences, Università Politecnica delle Marche, Ancona, Italy
[2]Allergy Unit, Department of Internal Medicine, University Hospital Ospedali Riuniti di Ancona, Ancona, Italy
[3]Allergy Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

Doi
10.23822/EurAnnACI.1764-1489.245

Hypersensitity reactions (HSRs) to iodinated contrast media (ICM) are classified into immediate reactions (IHRs) and non-immediate reactions (NIHRs) according to the time interval between ICM administration and appearance of symptoms, the first occurring within 1 (to 6) hours and the latter appearing more than 1 hour after the exposure, respectively. IHR may be of different severity, from urticaria and angioedema to reactions affecting the gastrointestinal, respiratory and cardiovascular systems and cardiovascular systems, sometimes with loss of consciousness (anaphylactic shock) (1, 2).
Maculopapular exanthema is the most frequent manifestation of NIHRs. More severe reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed drug eruption, drug reaction with eosinophilia and systemic symptoms, or acute generalized exanthematous pustulosis are less frequently observed. HSRs to ICMs have traditionally been considered as non-allergic, but growing evidence based on *in vivo* and in *vitro* tests points to immune mechanisms. According to a French study, the frequency of IgE-mediated allergy increases when three or four different organs are affected simultaneously, especially when cardiovascular symptoms appear in combination with respiratory or cutaneous reactions (3). Immediate, anaphylaxis-like reactions may be caused by an effect of the ICM on the mast cell membrane leading to mediator release (maybe through Mas-related G protein-coupled receptor member X2 (MRGPRX2)) or, possibly, by direct complement activation.
NIHR to ICM are characterized by a T-cell mediated mechanism, appearing from hours to days after administration of the ICM. Delayed appearing non-allergic urticaria and/or angioedema occurring > 6 hours after ICM administration seem to be caused by a different, poorly understood mechanism. In the past ionic ICM were used, with a prevalence of hypersensitivity reactions between 3.8% and 12.7% (4). With the introduction of nonionic ICM the prevalence has significantly decreased; however, over the last decade it has risen in parallel with their increased usage, ranging between 0.7% and 3% (5, 6). Severe IHRs as anaphylactic shock may also occur with nonionic ICM, even though with a frequency of 0.02%-0.04% and an estimated mortality rate of 1 in 100 000 examinations (5). However, no recent data are available on severe IHRs.
In this issue of *European Annals of Allergy and Clinical Immunology*, Cruz *et al*. (7) described three cases of anaphylactic shock following the use of ICM, putting the spotlight on the fact that severe, potentially fatal IHRs continue to occur, despite the use of low-osmolar ICM. As recently pointed out by the EAACI Position Paper (1) radiologists have to know they can experience this type of reaction, they should improve emergency awareness and training on emergency treatment of ICM IHR, and take a blood sample for the measurement of tryptase level. Moreover, they should contact the allergist for future patient management.
The main risk factor for IHR and NIHR seems to be a previous severe reaction to ICM. A previous IHR does not increase the risk for an NIHR and vice versa. Other presumed predisposing factors (like female gender, renal insufficiency, a history of doctor-diagnosed asthma, drug allergy, food allergy, contact allergy for NIHRs, and interleukin-2 treatment for NIHRs) as well as repeated exposures to ICM (**table I**) have not been confirmed in all studies, which are often dated, and therefore cannot be used as pre-requisite for performing ICM allergy work-up (1). Nevertheless, a better identification of the patients at risk could be of great utility to improve the safety of the procedures, and the articles of Voltolini (8) and Dellis (9) published in this issue of *European Annals of Allergy and Clinical Immunology* analyze this matter. Although both retrospective, these articles draw attention to the need to perform multicenter studies in order to confirm and/or identify new risk factors for severe ICM reactions and thus obtain a more precise risk stratification. In Voltolini's study, a large population (407) of Italian patients collected by 9 Allergy Units experiencing hypersensitivity reactions to ICM was compared with a control group of 152 subjects who tolerated one or more ICM-enhanced examinations. In line with other studies, a greater risk of HRSs in females and in patients under 65 years of age was observed (8). Moreover, it is of great interest that 35% of patients were on their first exposure, exactly in the

same percentage as in Dellis' study (9). In this study only 16% of the reactive group reported one or more previous ICM adverse reactions. Cardio-vascular disease, adverse drug reactions and respiratory allergy (but not asthma) were identified as risk factors for ICM reactions (8). Indeed, in the literature as well as in this study the term "atopy" is misused, mainly being an anamnestic data, without confirmation by diagnostic tests.

Dellis' study analyzed the characteristics of 80 patients experiencing HS reactions to ICM with a focus on oncological status. Half of patients had a history of cancer; cancer was active in 80% of cases, among them 31% were under treatment at the time of the reaction. There were no statistically significant differences between oncological patients and non-oncological patients with HSR in relation to gender, age, cardiovascular disease or asthma, history of previous reactions to ICM, and, interestingly, number of previous exposures. However, they were characterized by a low incidence of personal atopy (9).

The following question comes up: could the oncological diseases and/or their specific treatments be a risk factor for reaction to ICM? There are currently insufficient data in the literature to answer this question. More than cancer itself, repeated exposure could increase the risk of adverse reactions in patients with cancer (10, 11) or perhaps the combination of both factors. In contrast, in Voltolini's study, a high number of oncologic patients were part of the control group without HSRs and were significantly more exposed to ICM-enhanced examinations in the last year. Moreover, antineoplastic treatments as potential risk factors of HSRs have been only hypothesized.

Finally, it is noteworthy that the suspected culprit agent is often unknown in clinical practice (about 40% of cases in Voltolini's study). It depends on the fact that documentation in radiology and cardiology departments does not report the ICM name in most cases. Interestingly, a significant difference in reporting the name of the culprit ICM was observed between university centers in the same country (9). Accurate documentation of the contrast agent that induced the response/reaction should be mandatory to allow a more precise allergological work-up and therefore a more effective management of the patient choosing a different agent or premedication (12). Another important action to reduce the incidence of ICM-hypersensitivity reactions include the use of low-dose ICM and injection speed rate (13). In conclusion, at the moment we do not have certainties on the risk factors of HSRs. We cannot exclude that these reactions may be due to the concomitant presence of multiple and specific factors in predisposed subjects. Therefore, larger multicentric prospective studies are needed to explore different risk factors, to stratify the risk of the individual patient and adopt the best possible prevention strategies to avoid future HSR.

Table I *- Some potential risk factors for hypersensitivity reactions to ICM.*

Patient risk factors	**Procedure risk factors**
Previous reaction to ICM	First administration
Female gender	Repeated administration
Age < 65	Previous exposure via intra-arterial route for intra-arterial ICM
Atopy	Higher dose
Asthma	Injection speed
Drug allergy	
Oncological disease	
Severe cardiovascular disease	

References

1. Torres MJ, Trautmann A, Böhm I, *et al*. Practice parameters for diagnosing and managing iodinated contrast media hypersensitivity. Allergy 2021;76(5):1325-39.
2. Sánchez-Borges M, Aberer W, Brockow K, *et al*. Controversies in Drug Allergy: Radiographic Contrast Media. J Allergy Clin Immunol Pract 2019;7(1):61-5.
3. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. Radiology 1990;175(3):621-8.
4. Clement O, Dewachter P, Mouton-Faivre C, *et al*. Immediate Hypersensitivity to Contrast Agents: The French 5-year CIRTACI Study. EClinicalMedicine 2018;1:51-61.
5. Brockow K, Christiansen C, Kanny G; ENDA; EAACI interest group on drug hypersensitivity. Management of hypersensitivity reactions to iodinated contrast media. Allergy 2005;60(2):150-8.
6. Schönmann C, Brockow K. Adverse reactions during procedures: Hypersensitivity to contrast agents and dyes. Ann Allergy Asthma Immunol 2020;124(2):156-64.
7. Cruz C, Tavares Semedo F, Mota I, Borrego LM. Anaphylactic shock to iodinated contrast media: not so rare after all. Eur Ann Allergy Clin Immunol 2022;54(2):95-6.
8. Voltolini S, Cofini V, Murzilli F, *et al*. Hypersensitivity reactions to iodinated contrast media in Italy: a retrospective study. Characteristics of patients and risk factors. Eur Ann Allergy Clin Immunol 2022;54(2):60-7.
9. Dellis P, Pirson F. Isn't it time to consider oncological status as a new risk factor of iodinated contrast media hypersensitivity? Eur Ann Allergy Clin Immunol 2022;54(2):68-76.
10. Fujiwara N, Tateishi R, Akahane M, *et al*. Changes in risk of immediate adverse reactions to iodinated contrast media by repeated administrations in patients with hepatocellular carcinoma. PLoS One 2013;8:e76018.
11. Lee SY, Kang DY, Kim JY, *et al*. Incidence and Risk Factors of Immediate Hypersensitivity Reactions Associated With Low-Osmolar Iodinated Contrast Media: A Longitudinal Study Based on a Real-Time Monitoring System. J Investig Allergol Clin Immunol 2019;29(6):444-50.
12. Deng F, Li MD, Wong A, *et al*. Quality of documentation of contrast agent allergies in electronic health records. J Am Coll Radiol 2019;16(8):1027-35.
13. Park HJ, Son JH, Kim TB, *et al*. Relationship between lower dose and injection speed of iodinated contrast material for CT and acute hypersensitivity reactions: an observational study. Radiology 2019;293(3):565-72.