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P. Dellis[1], F. Pirson[1,2,3]

Isn't it time to consider oncological status as a new risk factor of iodinated contrast media hypersensitivity?

[1]Department of Pulmonology, Cliniques Universitaires Saint-Luc, Brussels, Belgium
[2]Cliniques Universitaires Saint-Luc, Centre de l'allergie Saint-Luc, Brussels, Belgium
[3]Pole of Pulmonology, ENT and Dermatology, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium

Key words

Iodinated contrast media; drug hypersensitivity; risk factors; cancer; targeted therapies.

Corresponding author
Perrine Dellis
Department of Pulmonology
Cliniques Universitaires Saint-Luc
Avenue Hippocrate 10
1200 Brussels, Belgium
ORCID ID: 0000-0002-7871-4025
E-mail: dellisperrine@gmail.com

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Impact statement

This study finds an equivalent proportion of oncological and non-oncological patients in a population of patients with hypersensitivity to ICM. Oncological patients did not have other known risk factors, and they were less atopic suggesting a new risk factor.

Summary

Background. *The literature describes several risk factors for hypersensitivity (HS) reactions to iodinated contrast media (ICM).* ***Objective.*** *To analyze the characteristics of patients experiencing HS reactions to ICM with a focus on oncological status.* ***Methods.*** *All patients (n = 80) with suspected HS to ICM who underwent an allergy evaluation in a Belgian University Hospital over a 5-year period were retrospectively included.* ***Results.*** *Overall, forty patients (50%) had a history of neoplasia, and this group was characterized by less atopy (p < 0.004). No significant difference was observed between oncological and non-oncological patients in terms of gender, age, cardiovascular diseases, medical treatment, and number of previous exposures or reactions to ICM.* ***Conclusions.*** *A high proportion of oncological patients was observed in our population with HS to ICM. They did not have other known risk factors, and they were less atopic. Larger multicentric studies should explore cancer as a potential new risk factor.*

Introduction

Adverse reactions following the administration of iodinated contrast media (ICM) are a major concern for allergists and have been reported to occur in up to 3% of patients receiving nonionic ICM (1, 2). These events associated with ICM can lead to toxic reactions and immediate or delayed hypersensitivity (HS) reactions (2). The involvement of immune mechanisms was demonstrated over the past few decades in some of these HS reactions (3-5). In our daily practice, we have observed that oncological patients were frequently concerned by ICM HS reactions. Repeated exposures to ICM, which were previously described as risk factors, are particularly common in the oncological population (6, 7). Moreover, antineoplastic treatments as potential risk factors of these HS reactions have been the topic of some studies, although clear conclusions have yet to be drawn (8-11). The aim of our study was to analyze the characteristics

of patients evaluated for suspected ICM HS in our allergy unit while focusing on oncological status as a possible risk factor.

Materials and methods

This retrospective study included all patients who underwent an allergy assessment for a suspected ICM HS reaction (immediate or delayed) with the same specialist between January 2015 and December 2019 in the Department of Pneumology/Allergology of Cliniques Universitaires Saint-Luc (Brussels, Belgium). The evaluation was not limited to patients who experienced the reaction at our institution. The study was approved by the Commission d'Ethique Biomédicale Hospitalo-Facultaire UCL (2019/17JUL/325). Demographic and clinical data in addition to the findings of the allergy investigations were collected from medical records. Clinical symptom onset was classified as immediate (≤ 1 hour after administration) or delayed if occurring > 1 hour until 7 days later (12).
In the case of anaphylaxis (13), the severity level was defined by the Ring and Messmer classification (14). Immediate minor cutaneous manifestations (*e.g.*, isolated pruritus, localized urticaria), isolated malaise, or respiratory symptoms (*e.g.*, sneezing, nasal congestion, dyspnea, bronchospasm, cough) were considered to be non-anaphylactic isolated reactions. The severity of delayed reactions was classified according to Brockow *et al.* (2, 15).
Skin tests (ST) were performed in conformity with the European Academy of Allergy and Clinical Immunology (EAACI) recommendations (16, 17). Patients were initially tested with the suspected ICM. In the case of a positive ST, other available ICM were tested (ioxitalamate, ioxaglate, iopromide, iomeprol, iohexol, iobitridol, iodixanol) to document cross-sensitivity. If the nature of the suspected ICM was unknown while the observed reaction was highly suggestive of a true HS reaction, patients were tested with all the available ICM. Skin prick tests (SPT) were performed on the forearm with pure ICM commercial solutions combined with positive (histamine 10 mg/ml) and negative control tests (glycerinated solution). Intradermal tests (IDT) were then performed on the arm using 0.02 ml of 10-fold diluted solutions from 10^{-3} to 10^{-1} and a negative control IDT. To evaluate non-immediate hypersensitivity (NIHS) reactions in patients without delayed severe manifestations, IDT were performed with a reading from the 48th to 120th hours. Patients without well-documented atopy (n = 35) were also tested for common aeroallergens using standardized extracts (Stallergènes®, Antony, France). Latex sensitization was evaluated by SPT (Latex© ALK-Abelló solution, Almere, Netherlands). Chlorhexidine digluconate sensitization was screened by SPT and IDT (18). Both were also evaluated by specific IgE.
The level of total serum tryptase was measured by ImmunoCAP™ Tryptase (Thermofisher Scientific) in the acute phase and/or at the time of the allergy evaluation for the basal value (19).
Investigations were followed by a drug provocation test (DPT) for a subset of patients with manifestations suggestive of HS but with negative ST. ICM was administered intravenously every 30 minutes with increasing doses from a 10^{-2} diluted solution until reaching a tenth of the normal dose, adjusted for weight and renal function (20).
At the end of the allergy evaluation, patients were divided into different groups based on their clinical features and test results: 1) IgE-mediated immediate hypersensitivity (IHS) reactions proven by ST; 2) non-IgE-mediated immediate reactions with negative ST (pseudo-allergic group as suggested by Pichler (21)); 3) absence of hypersensitivity to ICM, including immediate reactions due to other mechanisms (type A reaction, panic attack, reaction due to another agent); 4) delayed reactions with immunological mechanisms proven by ST; and 5) delayed reactions with negative ST.

Statistical analysis

The normality of the distribution of the quantitative variables was tested the Shapiro-Wilks test. The parametric Student t test and non-parametric Mann-Whitney U test/Wilcoxon test were used to compare the means of independent serial data. The comparison of the distribution of qualitative criteria in two or more populations was performed using Fisher's exact test/Pearson's Chi-squared test. The limit of significance was set at $p = 0.05$. All statistical analyses were performed with the StatEL© software, version 2.17 (Ad Science Paris, France) and JMP pro software version 14 3.0 (jmp. Statistical Discovery™ from SAS, Cary USA).

Results

Eighty patients were evaluated for suspected HS following the administration of ICM. Their demographic data are shown in **table I**.
Overall, 31% of patients (n = 25) were referred by another institution: the median time interval before the allergy assessment was longer for these patients ($p < 0.01$) than for patients coming from our institution.
The culprit ICM was identified in 66 patients (82.5%): iobitridol (n = 39), iomeprol (n = 16), ioxitalamate (n = 8), iopromide (n = 4), iodixanol (n = 4), and ioxaglate (n = 2), while 7 patients received ioxitalamate concomitantly with another non-ionic ICM. The ICM was unknown for 14 patients (17.5%), 12 of whom came from other institutions ($p < 0.00001$).
At the time of the allergy workup, 36 patients (35%) were evaluated after a reaction on the first exposure, while the remaining 44 (55%) had been previously exposed to an ICM on at least one occasion. Among the 44 patients, 8 had already reported manifestations on the first exposure and 4 on another exposure (but without an allergy evaluation).
A total of 58 patients reported an immediate reaction (72.5%), while 21 had a non-immediate reaction (26.3%); for one patient, the chronology was imprecise.

Table I *- Demographic data of the population (n = 80).*

		P-value
Gender ratio, male/female, n (%)	29 (36.2)/51 (63.8)	
Patients referred from other institutions, n (%)	25 (31.2)	
Mean age at the time of the event, years ± SD	51.1 ± 17.2	
In our institution	55 ± 16.7	< 0.01 (Student test)
From other institutions	44 ± 15.5	
Median time between reaction and allergy assessment, months [min-max]	6 [0.75-396]	
In our institution	4 [0.75-185]	< 0.01 (Mann-Whitney)
From other institutions	36 [1-396]	
Cardiovascular disease, n (%)	39 (48,8)	
Personal atopya, n (%)	26 (32.5)	
Asthma	7 (26.9)	
Allergic rhinitis	12 (46.1)	
Known latex allergy prior the reaction	0 (0)	
Latex sensitization identified in ICM allergy assessment	4 (5)	
Neoplasia (active or past), n (%)	40 (50)	
Active neoplasia at the time of the incident	32 (80)	
Oncological treatment at the time of the incident	10 (25)	
Ongoing medical treatment, n (%)		
None	17 (21.25)	
ACE inhibitors or ARB	26 (32.5)	
Beta-blockers	22 (27.5)	
PPI	24 (30)	
Indication for ICM administration, n (%)		
Contrast-enhanced CT scan	64 (80)	
Coronary and peripheral angiography	8 (10)	
Intra-cavity opacification (arthrography, gynecological, digestive)	5 (6.2)	
Intravenous urography	2 (2.5)	
Unknown	1 (1.2)	
Previous exposure to ICM, n (%)	44 (55)	
Reaction on previous exposure	12 (27.2)	

[a]Documented previous allergy and asymptomatic patients with positive SPT; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; CT: computed tomography; ICM: iodinated contrast media; PPI: proton pump inhibitors.

Half of patients (n = 40) had a history of cancer. Cancer was active in 80% of cases (n = 32), and 10 patients were under treatment at the time of the reaction (5 on chemotherapy, 4 on targeted therapy, and 1 on immunotherapy). Their characteristics are described in **table II**. Oncological and non-oncological populations did not statistically differ in terms of age at the time of the incident, time interval to the allergy assessment, gender, previous exposure or history of a previous reaction with an ICM, as well as a reaction on the first exposure ($p > 0.05$). Personal atopy was more statistically frequent in the non-oncological group ($p < 0.004$).

In the immediate reaction group (n = 58) (**figure 1**), 24 patients (41.4%) reported manifestations consistent with anaphylaxis: 7 (12%) for grade 1, 10 (17%) for grade 2, 5 (9%) for grade 3, and 2 (3%) for grade 4. Furthermore, 34 patients (58.6%) described

Table II *- Characteristics of patients with and without a history of cancer.*

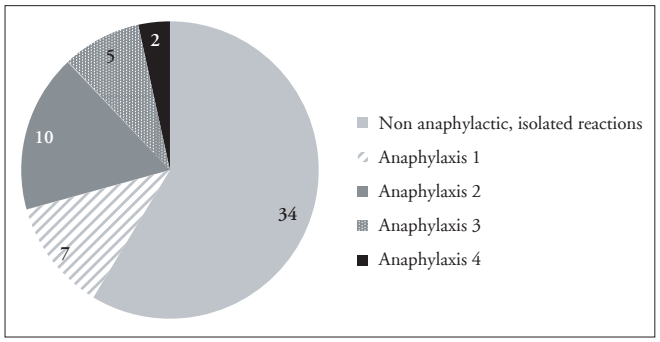
	Neoplasia (active or past) (n = 40)[a]	**No neoplasia (n = 40)**
Gender ratio, male/female, n (%)[b]	13 (32.5)/27 (67.5)	16 (40)/24 (60)
Median age at the time of the incident, years [min-max][b]	52 [18-85]	53 [9-80]
Median time until allergy assessment, months [min-max][b]	5 [1-180]	7.5 [0.75-396]
Cardiovascular disease, n (%)	18 (45)	21 (52.5)
Personal atopy, n (%)[c]	7 (17.5)	19 (47.5)
Rhinitis	3 (7.5)	9 (22.5)
Asthma	2 (5)	5 (12.5)
Latex sensitization	1 (2.5)	3 (7.5)
Previous exposure to ICM, n (%)[b]	25 (62.5)	19 (45.5)
Reaction on previous exposure	8 (20)	4 (10)
Current treatment, n (%)[b]		
ACE inhibitors or ARB	10 (25)	14 (35)
Beta-blockers	9 (45)	12 (30)
Chronology of reaction, n (%)[b]		
Immediate	30 (75)	28 (70)
Delayed	10 (25)	11 (27.5)
Unknown	0 (0)	1 (2.5)
Severity of immediate reaction, n (%)[b]		
Anaphylaxis grades 1-2	10 (25)	7 (17.5)
Anaphylaxis grades 3-4	5 (12.5)	2 (5)
Non-anaphylactic isolated reactions	15 (37.5)	19 (47.5)
Severity of delayed reaction, n (%)[b]		
Mild	3 (7.5)	7 (17.5)
Moderate	7 (17.5)	4 (10)
Positive ST to ICM, n (%)[b]	10 (25)	5 (12.5)
Immediate ST	6 (15)	3 (7.5)
Delayed ST	4 (10)	2 (5)

ACE: angiotensin-converting enzyme; ARBs: angiotensin II receptor blockers; ICM: iodinated contrast media; ST: skin test; [a]types of neoplasia were as follows: 11 digestive (27.5%), 8 urologic or gynecologic (20%), 7 hematologic (17.5%), 7 breast (17.5%), 5 lung (12.5%) and 5 (12.5%) other types of cancer. Three patients had multiple cancers; [b]between-group differences for the different criteria are not statistically significant (Mann-Whitney and Fisher exact tests, $p > 0.05$); [c]between-group difference is statistically significant ($p < 0.004$, Chi^2 test).

non-anaphylactic isolated reactions: 9 with isolated respiratory symptoms, 13 with local cutaneous manifestations, 3 with malaises, and 9 with other/unknown reactions). Non-immediate manifestations (n = 21) were mostly cutaneous (95%) of mild to moderate severity.

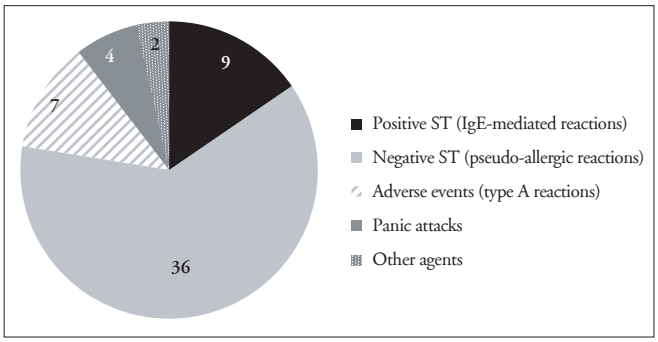
A total of 15 patients (18.75%) had a positive ST to at least one ICM associated with their culprit: 9 with immediate ST (60%) and 6 (40%) with delayed ST. ST with the suspected ICM were positive in 12 patients (80%) with iobitridol (7 immediate, 5 delayed), in 2 patients (13.3%) with iomeprol (1 immediate, 1 delayed), and in 1 patient (6.7%) with iopromide (immediate). For 2 patients, a responsible agent other than ICM was identified with ST and specific IgE (1 anaphylaxis of grade II to latex, 1 anaphylaxis of grade III to gelatin) (**figure 2**). A DPT also confirmed ICM HS in 2 patients (1 IHS, 1 NIHS).

Figure 1 *- Distribution of the clinical manifestations in immediate reactions (n = 58).*



The severity of anaphylactic reactions is graded according to the Ring and Messmer scale (14). Non-anaphylactic isolated reactions include local or mono-systemic symptoms such as isolated respiratory symptoms, local cutaneous manifestations, malaises, and other reactions/undetermined.

Figure 2 *- Classification of immediate reactions based on skin test results and symptoms (n = 58).*



Reactions to other agents refer to hypersensitivity to latex (n = 1) and gelatin (n = 1).

Personal atopy was found in 26 patients (32.5%) with at least one positive SPT for common aeroallergens (excluding latex). Latex sensitization, which was assessed by SPT (n = 30) and specific IgE (n = 12), was positive for 4 patients, who had a concomitant sensitization to at least one other aeroallergen. Sensitization to chlorhexidine was evaluated in 32 patients and was negative. No case of mastocytosis was suspected after the allergy evaluation.
In the immediate manifestation group, 14 patients who reported symptoms suggestive of grade 1 to 3 anaphylaxis had negative ST and were finally classified in the pseudo-allergic group (**figure 3**). Although the vast majority (95.6%) of patients with non-anaphylactic isolated symptoms (not attributed to panic attacks or adverse events) had negative ST, one patient nevertheless had positive ST. Both patients with grade 4 anaphylaxis had positive ST. For patients with non-immediate manifestations (n = 21), 28.6% had positive delayed ST, suggestive of a T-cell-mediated allergic mechanism.

Cross-sensitization

In patients with immediate positive ST (**table III a,** n = 9), 4 were mono-sensitized and 5 (55%) had at least one cross-sensitization documented by ST. All patients with positive delayed ST (**table III b**, n = 6), had at least one cross-sensitization. These allergic patients were advised to receive an ICM for which the ST were negative.

Re-exposure

Re-exposure to ICM occurred in 55% of patients (32 with immediate and 12 with delayed initial reactions) and was well tolerated for 97.7% of them: 31.8% were re-exposed to their culprit ICM with negative ST, 13.6% received an ICM tolerated during DPT, and 13.6% with positive ST received an alternative ICM for which they tested negative.

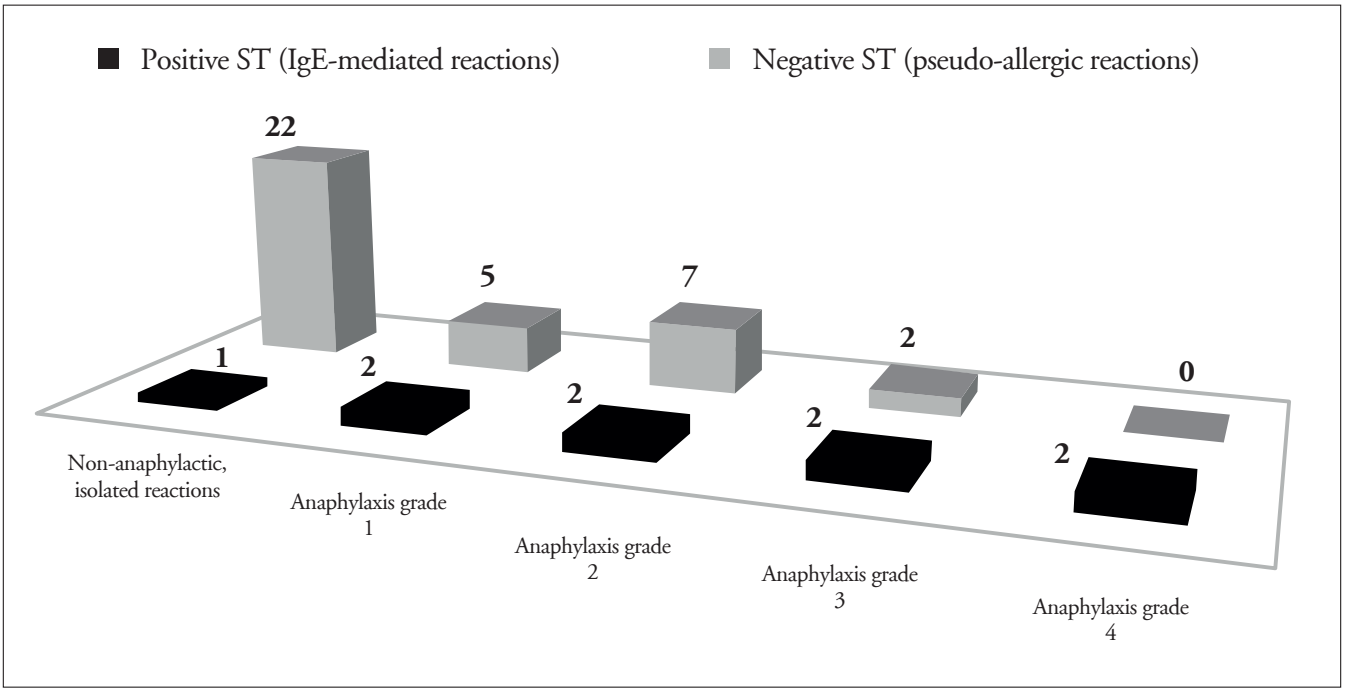
Subgroup analyses

Univariate analyses were conducted on the 45 patients from two sub-groups experiencing immediate reactions (group 1: IgE-mediated; group 2: IHS with negative ST "pseudo-allergic"), including several co-factors (gender, cardiovascular disease, age, history of active or past neoplasia, personal atopy, ongoing medical treatment, number of previous exposures and previous reactions to ICM). Patients with cardiovascular diseases (hypertension, ischemia, or valve disease) were significantly older at the time of the reaction than those without ($p < 0.02$). Nevertheless, none of the criteria were associated with a higher incidence of IHS reaction to ICM. Although drugs like ACE inhibitors, ARBs ($p < 0.0001$), statins ($p < 0.001$), and proton pump inhibitors (PPI) ($p < 0.05$) were more often prescribed to patients with cardiovascular diseases, cardiovascular risk was not identified as a risk factor of ICM IHS reaction in our study. Oncological patients (past and/or active cancer) with IHS (n = 21) did not differ statistically from non-oncological patients concerning gender, age, cardiovascular disease, number of previous exposures, history of previous reactions to ICM, or asthma. However, they were characterized by less allergic rhinitis ($p < 0.05$) and tendency toward less personal atopy ($p = 0.05$).

Discussion

Our study included 80 patients, including 58 with an immediate clinical reaction of HS to ICM, 21 with a delayed reaction, and 1 unclassifiable patient. An immunological HS to ICM was documented for 17 patients (21.3%): 15 patients by ST (18.75%) including 9 with an IHS and 6 with a NIHS, and 2 patients (2.5%) by DPT (1 IHS, 1 NIHS).
A high proportion of oncological patients was observed in our study. Indeed, 40 patients (50%) had a history of cancer at the time of the

Figure 3 *- Distribution of patients according to the severity of their immediate clinical reactions and the mechanism involved (n = 45).*



Reactions due to agents other than iodinated contrast media, panic attacks, and adverse events are excluded.

reaction. To our knowledge, in previous studies, oncological status was rarely mentioned in the population characteristics. Moreover, our oncological group did not have more known risk factors.

Risk factors for HS reactions to ICM are not fully established and are still matter of debate. In line with other authors, a recent multicentric Italian study comparing reactive and control groups reported female gender, age ≤ 65 years, first ICM exposure, cardiovascular diseases, and respiratory allergy to be significant risk factors for ICM HS in multivariate analysis (22). Previous studies also mention asthma, treatment with ACE inhibitors, beta-blockers, or proton pump inhibitors, previous or repeated ICM administrations, and mastocytosis to be risk factors (6, 23-27). The main risk factor seems to be a previous reaction, even if a significant number of subjects experienced HS to ICM on the first exposure (4, 22). In our study, no significant difference was observed in terms of gender, age, ongoing medical treatment, previous exposure, previous reaction, and reaction on the first exposure for oncological patients, although these results could be biased by our small population size. However, the oncological population was characterized by a lower incidence of personal atopy ($p < 0.004$). This suggests that oncological diseases and/or their specific treatment could be a risk factor for reaction to ICM.

In the literature, cancer and/or its treatment have not yet been clearly identified as risk factors, as these topics have been poorly studied to date. The incidence of IHS reactions to ICM was higher in patients with cancer (2.1% *vs* 1.1% for patients without cancer, $p < 0.001$) in a cohort of 86,328 patients (23) who underwent an enhanced computed tomography (CT) scan, but evidence is lacking regarding the association between oncological status and HS reactions to ICM. Repeated administrations of ICM are common in the oncological population and may lead to a higher risk of adverse reactions. Fujiwara *et al.* (7) retrospectively reviewed 1,861 patients with hepatocellular carcinoma and showed an increased risk of adverse reactions with repeated exposures. In our study, even though oncological patients were exposed to ICM more frequently but not significantly compared to non-oncological patients (62.5% *vs* 45.5%, $p > 0.05$), previous reactions were not reported more often (20% *vs* 10%, $p > 0.05$). In our recent survey, 10 patients (8%) who experienced HS reactions to ICM were receiving oncological treatment at the time of the event, with half of them under immunotherapy or targeted therapy. The association between oncological treatments and the risk of adverse reactions to ICM has been the topic of very few studies. Farolfi *et al.* (8) reviewed 1,878 cancer subjects who underwent a contrast-enhanced CT scan within 30 days of their last chemotherapy and did not find any correlation between time to CT and the risk of acute ICM adverse reactions. Concomitant treatment with taxane-based chemotherapy was reported as a risk factor for acute adverse reactions to ICM compared to the non-treatment group in a cohort of 3,804 oncological patients (9). Few cases of anaphylaxis in oncological patients

Table III *- Cross-sensitivity patterns for patients with immediate* ***(a)*** *and delayed* ***(b)*** *hypersensitivity (HS) reactions to iodinated contrast media (ICM).*

a (n = 9)	**Immediate HS**							
	Cross-sensitivity							
Culprit ICM	Ioxitalamate	Ioxaglate	Iopromide	Iomeprol	Iohexol	Ioversol	Iobitridol	Iodixanol
Iopromide (n = 1)								
Iomeprol (n = 1)					A1			A1
Iobitridol (n = 7)			A3, A6, A8	A7				A6
b (n = 6)	**Non-immediate HS**							
	Cross-sensitivity							
Culprit ICM	Ioxitalamate	Ioxaglate	Iopromide	Iomeprol	Iohexol	Ioversol	Iobitridol	Iodixanol
Iomeprol (n = 2)			B4		B4		B1	B4
Iobitridol (n = 4)			B2, B3, B5	B2, B3	B5			B2, B3, B5, B6

treated with immunotherapy following a contrast-enhanced CT scan have also been described (10, 11), particularly ipilimumab and nivolumab. As these therapeutic options are relatively recent, it could be a new risk factor to monitor. Interestingly, personal atopy was observed significantly less in our oncological group ($p < 0.004$). Moreover, this was confirmed for oncological patients with IHS in whom allergic rhinitis was less frequent ($p < 0.05$). Previous studies (28-32) obtained mixed results about the association between atopic diseases and the risk of cancer.

For example, asthmatic patients had a greater risk of cancer, including lung cancer (33), although the phenotype seemed to play a major role as the incidence of cancer was higher in non-atopic than in atopic asthma (34). Nevertheless, the dominant picture emerging from the majority of epidemiological data (28, 32, 35, 36) indicates that several atopic diseases (asthma, atopic dermatitis, and allergic rhinitis) were associated with a lower incidence of cancer, which supports our results.

The sensitivity of ST varies widely among studies, ranging from 4.2% to 73% (4, 5, 22, 37-44) depending on the clinical severity and the time interval between the reaction and ST. A meta-analysis of 21 studies (45) showed positive ST rates of 17% in patients with IHS reactions and up to 52% when limited to severe IHS reactions. In a prospective multicentric study (4), ST were positive for 50% of IHS and 47% of NIHS reactions when performed within 6 months after the reaction, dropping to 18% for IHS and 22% for NIHS reactions investigated after 6 months. Our rate of positive ST could be explained by the large proportion of patients (87.9%) with light and mild immediate symptoms (non-anaphylactic with isolated reactions and grades 1-2 of anaphylaxis). Nevertheless, it was interesting to note that these symptoms could rarely be induced by immunological mechanisms (8.6%). This was previously reported by Clement *et al.* (44) and could probably be an argument to perform an allergy evaluation even if the symptoms are minor. As in previous studies (37, 39, 42-44), several cases of severe anaphylaxis (≥ grade 3) following ICM administration had negative ST. New concepts to explain non-IgE-mediated anaphylactic reactions to ICM are emerging such as the Mas-related G protein-coupled receptor X2 (MRGPRX2) (21, 46).

Our rate of positive ST was also influenced by the time until allergy workup, as nearly half of patients (48.75%) were evaluated within 6 months of the event, and ST were positive in 30.8% of cases, falling to 7.3% after this time. This interval was significantly longer for patients who developed their reaction in another institution, which was further characterized by a higher proportion of unknown administered ICM (48% *vs* 3.6% in our institution). DPT was useful to highlight a possible immunological mechanism for a subset of patients (2.5%) with negative ST. Nevertheless, this procedure was not systematically

performed, and there is still no consensus regarding its role in the diagnostic algorithm of ICM HS (47, 48).
Several examples of cross-sensitivity have been described in the literature (4, 5, 37, 38, 40-43, 49, 50) with various patterns and may be observed in up to 69% of NIHS reactions, less commonly in the case of IHS. It has been reported that iobitridol showed less cross-sensitivity than other ICM in the case of NIHS (51). We found cross-sensitivity in 11 patients (73.3%), 5 with IHS and 6 with NIHS. Iobitridol was the most reported culprit ICM in our study and frequently involved in cross-sensitivity reactions (81.2%), contrary to previous studies where it was also administrated less often. In fact, it is the most commonly used ICM in our institution, representing almost 60% of ICM administrations.

Conclusions

In conclusion, our study was characterized by a particularly large oncological population of patients with HS reactions to ICM. It is difficult to confirm whether cancer and its treatment are risk factors of these events, as we were limited by the small population size. In the future, greater attention should be given to emerging oncological therapies, which could be new potential risk factors. These topics should be investigated in larger multicentric studies with cohorts of both oncological and non-oncological patients. We need evidence to prove that the risk is not only due to the number of previous exposures or previous reactions to ICM in the oncological group. The role of atopy should also be evaluated in this particular population.

Contributors

PD: collection, analysis and interpretation of data, redaction of the manuscript. FP: acquisition, statistical analysis of data, supervision and critical revision of the manuscript.

Conflict of interests

The authors declare that they have no conflict of interests.

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