

T cell-mediated reactions to iodinated contrast media: Evaluation by skin and lymphocyte activation tests

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Background: In addition to immediate reactions, late adverse reactions to iodinated contrast media (ICM) were reported in 2% to 5% of patients exposed to ICM and, as a consequence, have recently gained more attention. A few well-documented case reports postulate a hypersensitivity mechanism.

Objective: The aim of this study is to demonstrate a T cell-mediated mechanism to the ICM by using *in vitro* and *ex vivo* tests.

Methods: We analyzed 12 patients with 13 adverse ICM reactions, 9 of whom were women. Clinical history suggested an immune reaction to ICM. Skin tests (skin prick, intradermal, and patch tests) were performed with various ICM and read after 15 minutes and 24 and 48 hours. Skin biopsy specimens of positive test sites of 11 patients were evaluated by means of immunohistology. T-cell reactivity to ICM *in vitro* was analyzed with lymphocyte activation tests.

Results: Seven patients showed generalized maculopapular eruptions, one of them with fever; 4 had a so-called drug hypersensitivity syndrome with exanthema, eosinophilia, and fever; 1 had maculopapular eruptions and fever; 1 had late-onset urticaria with loss of consciousness; and 1 had facial edema and respiratory distress. An immune reaction to ICM was inferred from positive skin prick test (2 patients), positive patch test (10 patients), and positive intradermal test (9 patients) at 24 and 48 hours. Skin biopsy specimens revealed a T-cell infiltrate in the dermis with predominantly CD4⁺ T cells in 8 patients, CD8⁺ T cells in 1 patient, and equal numbers in 1 patient. Cross-sensitivities to several ICM were observed (9/12). Other drug allergies were noted in 6 of the 12 patients. **Conclusions:** Delayed reactions to ICM are most likely caused by immune reactions to these drugs and can elicit different clinical features. The involvement of T cells is suggested by positive skin test, as well as positive proliferative responses, to the drugs *in vitro*. A high degree of cross-reactivity with other than the eliciting ICM was observed. Moreover, 50% of these

patients reported another drug hypersensitivity, suggesting a predisposition to immune reactivity in some patients. (J Allergy Clin Immunol 2005;115:179-85.)

Key words: Adverse drug reaction, drug allergy, iodinated contrast media, patch test, intradermal test, T cell-mediated hypersensitivity, cross-sensitivity, multiple drug allergy

Iodinated X-ray contrast media (ICM) is among the most frequently used pharmaceuticals. Most adverse reactions produced by ICM occur shortly after the administration of the agent and are toxic and possibly allergic reactions of the immediate hypersensitivity type.^{1,2} On the other hand, late reactions to ICM have been reported for 2% to 5% of patients.³⁻⁶ They are defined as reactions occurring 1 hour to 1 week after contrast medium injection.^{7,8} The majority of late adverse reactions are cutaneous reactions, with itching, maculopapular rash, urticaria, and angioedema, as well as fever.⁹ More severe eruptions, although rare, have been reported, including multiform erythema,¹⁰ fixed drug eruption,¹¹⁻¹³ cutaneous vasculitis,^{14,15} Stevens-Johnson syndrome,¹⁶ toxic epidermal necrolysis,¹⁷ hypersensitivity syndrome,^{18,19} and sometimes life-threatening reactions.^{20,21} Patients at increased risk are those with a history of previous reactions and those receiving IL-2 treatment.²² A few well-documented case reports point to a delayed-type hypersensitivity indicated by positive late skin test responses.^{19,23-27}

Over the past few years, there has been increasing evidence that the majority of the late-onset skin reactions are mediated by T cells.^{8,9} In this study we report 13 T cell-mediated reactions to ICM in 12 patients and demonstrate the involvement of ICM by means of skin tests and immunohistologic studies of biopsy specimens, as well as lymphocyte transformation tests (LTTs).

METHODS

Patients

The clinical features of the patients are shown in Table I. Twelve patients (9 women and 3 men) with a mean age of 57 ± 17 years were evaluated after an adverse reaction to ICM. One patient (patient G) had similar late adverse reactions to the same ICM at a time interval of 7 years. The history took into consideration any intake of concomitant medications during the procedure, as well as any history of previous drug hypersensitivity. The allergy checkup was performed in

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TABLE I. Clinical features of patients who have presented a delayed reaction to ICM

Patient	Age (y)	Occupation	Sex	Clinical picture	Onset	Duration	Risk factors	Associated delayed-type drug hypersensitivities
A	76 y	Housework	F	MPE	24 h	2 wk	None	None
B	49 y	Nurse's aide	F	MPE	24 h	10 d	None	None
C	44 y	Secretary	F	Urticaria, loss of consciousness	5 h	24 h	None	Nalidixic acid
D	50 y	Worker in textile industry	F	MPE	10 h	2 d	Cardiac graft, several coronarographies, β -blockers	None
E	83 y	Housework	F	MPE	24 h	3 wk	None	None
F	59 y	Housework	F	MPE desquamative	24 h	3 wk	None	Pivalate tixocortol
G	63 y	Retired dental assistant	F	MPE, fever, blood eosinophilia	24 h	2 wk	β -blockers	None
G, second reaction	71 y			MPE, purpura, fever, kidney failure, pulmonary interstitial syndrome	3 d	2 wk	None	None
H	60 y	Postman	M	MPE, fever	48 h	4 d	5 scans in 3 mo	Ornidazole, piperacillin
I	41 y	Commercial representative	F	Facial edema, respiratory discomfort	Immediate	2-3 h	None	None
J	71 y	Nurse	F	MPE	18 h	3 wk	Cardiopathy, β -blockers	Ceftriazone, lugol
K	19 y	College student	M	MPE, fever, eosinophilia	1 h	2 wk	7 scans in 3 mo	Hydroxyzine
L	59 y	Restaurant worker	M	Erythema, asthma, eosinophilia	12 h	48 h	Several scans and arteriographies	Amoxicillin, cephalosporins

MPE, Maculopapular eruption.

Abbreviations used

ICM: Iodinated contrast media
 IDT: Intradermal test
 LAT: Lymphocyte activation test
 LTT: Lymphocyte transformation test

accordance with the previously published European recommendations.^{28,29} Experimental procedures, including the LTTs performed on patients and control subjects, were approved by the local ethics committee.

Skin testing

To search for an atopic predisposition, we carried out skin prick tests to common inhalant allergens.

Skin tests to ICM were performed according to the previously published method.^{19,28} Skin prick tests with undiluted ICM were followed by intradermal tests (IDTs) with different concentrations of ICM (first a 10^{-3} dilution and then a gradual increase to the undiluted ICM). If immediate readings were negative, patch tests were performed to the undiluted ICM.

The ICM tested were sodium meglumine amidotrizoate (Radiosélectan and Angiographine, Schering), meglumine ioxitalamate (Télébrix, Guerbet), ioxaglate meglumine and ioxaglate sodium (Héxabrix, Guerbet), iopamidol (Iopamiron, Schering), iobitridol (Xénétix, Guerbet), iopentol (Ivepaque, Nycomed), iohexol (Omnipaque, Nycomed), ioversol (Optiray, Guerbet),

iopromide (Ultravist, Schering), iodixanol (Visipaque, Nycomed), and iomeprol (Iomeron, Altana). Results were read after 15 minutes, 24 hours, and 48 hours. Skin prick tests were performed on the volar forearm, and a diameter of greater than 3 mm was considered a positive response for an immediate reading at 15 minutes, with a negative response to the control saline. IDTs were performed by means of the injection of 0.02 to 0.04 mL, raising a papula of 3 to 4 mm on the back. An increase in diameter of greater than 3 mm is considered a positive response for the immediate reading at 15 minutes.²⁸ Positive late reactions for IDTs consisted in an erythematous infiltration at the injection site 24 to 48 hours later. The patch tests were read according to International Contact Dermatitis Research Group recommendations.

The skin testing method was validated for all tested contrast agents in 20 exposed subjects who did not experience reactions. For ethical considerations, skin tests were not performed in nonexposed subjects. The results of skin prick tests, IDTs, and patch tests to ICM were negative in all control subjects.

Tests were also carried out with any concomitant medications reported in the interview: amoxicillin, piperacillin, ceftriazone, nalidixic acid, ornidazole, tixocortol, hydroxyzine, and lugol.²⁸

Immunohistology

Biopsy specimens from 11 patients were obtained, of which 10 were evaluated by means of immunohistology. Paraffin-embedded sections were studied with anti-CD3 (Novo); anti-CD45RO, anti-CD45RA, anti-CD8, anti-CD20, and anti-CD68 (Dako); anti-CD4 (Novocastra); and anti-CD1a (Immunotech) antibodies. Frozen sections were studied with anti-IgM (Silenus) and anti-IgA, anti-IgG, anti-C1q, anti-C3, and anti-C4 (Dako) antibodies.

Lymphocyte activation test

PBMCs from patients were obtained with Ficoll-Hypaque gradient and cultured with contrast media at 4 concentrations (0.1, 1, 10, and 100 mg/mL) that were shown to be nontoxic for PBMCs. For patients I, J, K, and L, the LTTs were performed with tritiated thymidine uptake into DNA after a cell culture period of 6 days.²⁹ In 2 patients (E and G) the proliferation was measured by means of cell-cycle analysis through measurement of DNA content,³⁰ and in patient G (second reaction) and in patient H, T-cell activation were measured by means of upregulation of the activation marker CD69 (double immunofluorescence).³¹

RESULTS

Clinical picture

Time to onset varied between 1 and 48 hours, except for in patient I, who displayed an immediate reaction with positive patch test and LTT responses to amidotrizoate. Reactions lasted between 2 hours and 3 weeks.

Clinical pictures included 6 generalized maculopapular eruptions, 4 hypersensitivity drug syndromes with eosinophilia and fever, 1 maculopapular eruption with fever, 1 urticaria with loss of consciousness, and 1 immediate reaction with facial edema and respiratory distress.

Certain patients presented with particular signs. Patient G, whose case report has been published previously,¹⁹ presented with a delayed-type hypersensitivity to ioxaglate in 1996, with fever, cytolytic hepatitis, and eosinophilia. Seven years later, in 2002, she was injected with the same iodinated contrast agent (ioxaglate meglumine and ioxaglate sodium) during coronary angiography, although she informed the staff of the previous hypersensitivity reaction and presented her allergy records. A fever (temperature of 39°C) developed as before, with maculopapular and purpuric eruption, diarrhea, renal insufficiency, cough, and pulmonary interstitial syndrome with hypoxia at 72 mm Hg that resolved with systemic corticosteroid therapy (patient G, second reaction).

Patient D presented with rash, although she was taking cyclosporine (200 mg/d) and systemic corticosteroids (5 mg of prednisolone).

Patient C experienced urticaria and loss of consciousness at 5 hours, and patient I experienced immediate facial edema and respiratory discomfort with symptoms evocative of anaphylaxis in spite of the presence of a delayed skin test reaction.

The predisposing factors found were repeated use of ICM for 5 patients (patients J, K, L, C, and G) and concomitant intake of β -blockers for 3 patients (patients D, G, and J).

Skin testing

Results of skin testing are shown in Table II. Skin test responses were positive at 24 hours for 5 patients and at 48 hours for 7 patients. The diagnosis was established on the basis of positive IDT for 3 patients, positive patch test for 4 patients, positive patch test and IDT for 3 patients, and positive skin prick test, patch test, and IDT for 3 patients.

Three patients were sensitive only to the ICM used, whereas 9 showed cross-sensitivities to other types of ICM.

An additional delayed-type hypersensitivity reaction to another medication was inferred from clinical history and skin tests in 6 patients (Table I).

Atopic predisposition was found in 2 patients.

Immunohistologic study

The results of immunohistologic study are shown in Table III. We obtained histologies from the acute reaction, as well as from the patch test reaction. The histology was compatible with a T cell-mediated reaction with a lymphocyte-rich cell perivascular infiltrate. The main lymphocyte population was composed of CD45⁺ cells of the T phenotype (CD45Ro and CD3⁺), with very rare CD45Ra⁺ cells (<20%). It consisted mainly of CD3-CD4 cells, with the exception of patients G and K, in whom an equal number of CD8 cells were found. The semiquantitative evaluation of CD1a⁺ cells was normal, except for in patients E and K (IDT), who presented with large numbers of Langerhans cells inside the epidermis and very few in the dermis. Eosinophils were absent or very rare. Discrete spongiosis was recorded in 5 patients. There was no staining with anti-IgA, anti-IgG, anti-IgM, anti-C1q, anti-C3, and anti-C4.

Lymphocyte activation and transformation tests

The lymphocyte activation test (LAT) measured by means of cell-cycle analysis through DNA content was positive to ioversol (the culprit ICM) and negative to iomeprol for patient E. The LAT measured by means of upregulation of the activation marker CD69 was positive to the culprit ICM for patient G (second reaction) and to amidotrizoate. The LAT was negative for patient H.

The LTTs were positive for 3 of 4 patients (Fig 1). The LTT response of patient L was strongly positive to iohexol (the culprit ICM), negative to iodixanol, and slightly positive to iopentol. A slight positivity of this test response (stimulation index up to 4) was also observed in 2 of 10 individuals not exposed to ICM. Thus the cutoff value was set at a stimulation index of 4 to be considered positive.

DISCUSSION

Clinical pictures of hypersensitivity to ICM vary greatly. In this article the term *allergy* is not limited to IgE-mediated allergy. Indeed, it is defined by the European nomenclature as an immune hypersensitivity without presumption of the immunopathogenesis.³² The maculopapular eruptions progressing later to desquamation observed here correspond to data in the literature. A characteristic feature of these eruptions is their location on the palms of the hands and secondary desquamation. The frequency of drug allergies associating fever and eosinophilia was highlighted (4 patients). This might be associated with severe organ impairment: hepatic cyto-

TABLE II. Results of skin tests (boldfacing indicates involved ICM)

Patient	Involved ICM	Ionic		
		Monomer		Dimer
		Amidotrizoate	Ioxitalamate	Ioxaglate
A	Ihexol	—	—	—
B	Ixitalamate	—	Pa⁺	—
C	- Iopamidol, + Iohexol, - Iobitridol	—	—	—
D	Iodixanol	—	—	—
E	Ioversol	—	—	—
F	Iomeprol	ND	IDT, Pa +	IDT +
G	Ioxaglate	—	IDT +	IDT +
G, second reaction	Ioxaglate	IDT +	IDT, Pa +	IDT, Pa +
H	Iobitridol	—	SPT, IDT, Pa +	SPT, IDT, Pa +
I	Probably amidotrizoate	Pa +	—	—
J	Iohexol	—	Pa +	Pa +
K	Iohexol, iobitridol	—	—	—
L	Iohexol	—	IDT, Pa +	IDT, Pa+

ND, Not done; Pa, patch test; SPT, prick test.

lytic damage, renal insufficiency, and respiratory impairment. The predominance of women reported in earlier studies was also found in our study.^{7,33} Late adverse reactions occurred from 1 hour to 2 days after administration but have been reported to occur up to 7 days after administration.^{7,8} It is interesting to note that in our series we have a patient presenting with an immediate reaction with an already demonstrated T cell-mediated mechanism (positive patch test and LTT response). On the other hand, we note that the duration of most of the reactions presented in these series is rather long, up to 3 weeks, whereas most skin reactions are considered to be resolved within a week in previously published studies.⁸

Certain associated factors might be risk factors. Repeated radiologic examination with ICM favors sensitization. The incidence of late adverse reactions after administration of ICM might increase in the future because of the increased use of ICM and the frequent re-exposure of patients to the same ICM or a structurally similar one. Three patients were taking β -blockers. This risk factor is known for immediate-type reactions³⁴ and highly suspected for delayed-type hypersensitivity.¹⁹ Atopy has been suggested as a predisposing factor.³⁵ It seems not to have been the case in this study because the frequency of atopic predisposition (16%) is identical to that of the general population.

The symptoms were similar to drug-induced adverse reactions, which have been shown to be T-cell mediated.³⁶⁻³⁸ These observations underline the role of T lymphocytes in inducing delayed reactions to ICM. Furthermore, it has been shown that treatment with recombinant IL-2 increases the frequency of delayed reactions to ICM.^{22,39} The positive prick test, IDT, or patch test responses with delayed reading and positive LTT demonstrate this. The histopathology of skin eruptions and positive skin test responses were compatible with a T cell-mediated mechanism. The histology was comparable with that previously seen in macular eruption, with predominantly perivascular lymphocytic infiltration of the

dermis, intraepidermal spongiosis, and eosinophilia as possible additional features.^{27,40,41} Positive skin test responses show the same histologic pattern.^{23,27,41,42} The histology was quite different from the case of fixed drug eruption, which has been reported as being characterized by lymphocytic infiltration of the dermis and epidermis, epidermal spongiosis and necrosis, eosinophilia, and degeneration of the basal layer but also by neutrophilic abscess in the stratum corneum.^{13,40} In the case of Stevens-Johnson syndrome, dermal lymphohistiocytic infiltrates and focal epidermal necrosis with blister formation were observed.¹⁶ Leukocytoclasia and a peripheral infiltrate of neutrophils around vessels were shown in a case of acute vasculitis.¹⁵ The mononuclear infiltrate was composed of activated T cells, mainly CD4⁺ T cells. One case of exocytosis of CD8⁺ T cells was reported for a patient with multiple fixed drug eruption.¹³ As previously reported, CD4⁺ cells tend to be associated to a morbilliform rash, whereas a substantial expansion of CD8⁺ cells is more likely to produce a bullous reaction.^{37,43}

Skin prick tests, IDTs, and patch tests all demonstrate this mechanism. Carrying out skin prick tests, IDTs, and patch tests simultaneously is supported by the fact that results can be discordant. The discrepancy observed between 2 techniques cannot be explained and demonstrates that both techniques are required to make a diagnosis. No difference in histologic appearance was observed in the biopsy specimens, irrespective of test techniques (ie, prick tests, IDTs, or patch tests). Histology is comparable with that of the eruption when a biopsy was carried out. T cell-mediated reactions to ICM appear not to be related to the class of ICM. Ionic, nonionic, monomeric, and dimeric agents have been involved in the late reactions described in this series. The frequency of cross-sensitivity to different ICM is worth noting^{7,10}; it concerns 75% of cases, which is different to immediate allergic reactions.¹ Cross-reactivity exists between ionic and nonionic, monomeric, and dimeric agents. Patient G demonstrated the specificity and relevance of causative

Nonionic							
Monomer							Dimer
lopamidol	lopentol	lohexol	loversol	lopromide	lobitridol	lomeprol	lodixanol
–	ND	Pa ⁺	ND	ND	–	ND	Pa ⁺
–	ND	–	ND	ND	ND	ND	ND
SPT, IDT, Pa +	SPT, IDT, Pa +	SPT, IDT, Pa +	Pa +	–	–	–	SPT, IDT, Pa ⁺
–	IDT +	IDT +	–	–	–	–	IDT +
–	ND	–	IDT +	ND	ND	ND	ND
IDT +	IDT +	SPT, IDT, Pa +	SPT, IDT, Pa +	Pa +	–	SPT, IDT, Pa +	–
IDT +	ND	–	ND	ND	ND	ND	ND
IDT, Pa +	IDT, Pa +	IDT, Pa +	IDT, Pa +	IDT, Pa +	IDT +	ND	Pa +
SPT, IDT, Pa +	SPT, IDT, Pa +	SPT, IDT, Pa +	SPT, IDT, Pa +	–	–	–	SPT, IDT, Pa +
–	ND	ND	ND	ND	–	ND	–
Pa +	Pa +	Pa +	Pa +	Pa +	Pa +	ND	Pa +
–	IDT, Pa +	IDT, Pa +	IDT, Pa +	IDT, Pa +	IDT, Pa +	ND	IDT, Pa +
IDT+	IDT+	IDT, Pa+	IDT, Pa +	IDT, Pa +	Pa +	ND	IDT, Pa +

TABLE III. Immunohistology of skin biopsy specimens

Biopsy site		Perivascular infiltrate of mononuclear cells in the dermis*	Exocytosis of mononuclear cells in the epidermis	CD4/CD8	LTT
A	Skin eruption; patch test	++	++	90/10	ND
B	Patch test	+	+	90/10	ND
D	IDT	+, rare eosinophils	+	80/20	ND
E	IDT	+	+, numerous CD1a ⁺	80/20	Positive ioversol
F	IDT	+	–	70/30	Negative iomeprol
G	Skin eruption; IDT	++	–	50/50	ND
G, second reaction	Skin eruption; IDT	+, numerous eosinophils; +, rare eosinophils	–	70/30	Positive ioxaglate, amidotrizoate
H	Prick test; IDT; patch test	+++	+++	60/40	Negative iobitridol, iohexol
I	Patch test	+, rare eosinophils	–	80/20	Positive amidotrizoate
J	Patch test	+	–	–	Positive iohexol
K	IDT	+, rare eosinophils	+ numerous CD1a ⁺	50/50	Negative iohexol, iobitridol
L	Patch test	+, rare eosinophils	–	60/40	Positive iohexol

*The lymphocyte population of the perivascular infiltrate of all biopsy specimens is CD45⁺, CD45Ro⁺, and CD3⁺, with rare CD45Ra⁺.

diagnosis by means of a positive skin test response: 7 years later, rechallenge with an injection of the same ICM induced a more severe drug allergy syndrome, as reported in the literature.^{13,17,18,25,27,42} The fact that late-onset hypersensitivity recurred 7 years after the first incident demonstrates the persistence of reactivity over time. In this patient successive allergy checkups indicated the onset of new cross-sensitivities (amidotrizoate and iohexol).

Conversely, negative skin test to ICM, as well as LAT, cannot be interpreted with any certainty. Case report A showed that the patient was allergic to iohexol, yet the same patient did not react to iobitridol and iopamidol: skin test responses were positive to iohexol but negative to the 2 ICM previously tolerated. Case report H showed that the reaction occurred after an injection of iobitridol, whereas the skin test and LAT responses were negative with this ICM.

The abnormal frequency of associated drug allergies is demonstrated for the first time: half the patients in our series (6/12) displayed various delayed-type drug hypersensitivities. These patients with another drug allergy presented with a pattern of cross-sensitivity to several ICM types. The hypothesis of a predisposition of some patients to lymphocyte activation by haptens could be envisaged. These reactions draw attention to the multiple drug hypersensitivity syndrome.^{44,45} T cell-mediated reactions to ICM appear to be part of a multiple drug sensitivity syndrome and might indicate a predisposition of some subjects to immune reactions to chemical substances. It should be added that in these cases, it is a delayed-type drug hypersensitivity and T cell-mediated reaction to ICM.

Both radiologists and patients should be aware that ICM might cause late adverse reactions that could develop even several days later. The patient should be informed of

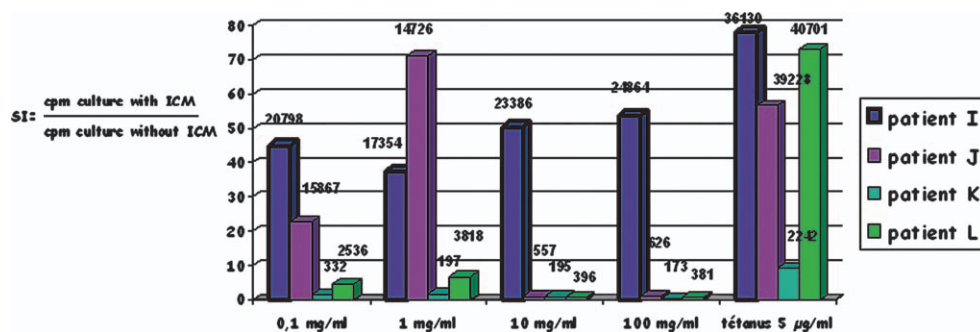


FIG 1. LTT. Counts per minute in the lymphocyte thymidine incorporation are noted on top of each bar.

the ICM used and advised to consult an allergy specialist to investigate any reaction.⁷ Radiologists should record the name of the ICM used in the patient's medical file,¹ especially if the patient needs to undergo repeated injections. The clinical relevance of any cross-sensitivity frequently noted during skin tests requires further study.

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