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

Gisèle Kanny, MD, PhD,[a] Werner Pichler, MD,[b] Martine Morisset, MD,[a] Patricia Franck, MD,[c] Béatrice Marie, MD,[d] Chantal Kohler, MD,[e] Jean-Marie Renaudin, MD,[a] Etienne Beaudouin, MD,[a] Jean Sainte Laudy, MD, PhD,[f] and D. Anne Moneret-Vautrin, MD[a] *Nancy, Vandoeuvre-lès-Nancy, and Paris, France, and Bern, Switzerland*

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.
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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

From [a]the Department of Internal Medicine, Clinical Immunology and Allergology, [c]Biochemistry, and [d]Anatomopathology, University Hospital, Hôpital Central, Nancy; [b]the Division of Allergology, clinic for Rheumatology and Clinical Immunology/Allergology Inselspital, Bern; [e]the Laboratory of Immunology, Faculty of Medicine, Vandoeuvre-lès-Nancy; and [f]the Laboratory of Immunology and Allergology, Paris.
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Reprint requests: Gisèle Kanny, MD, PhD, Médecine Interne, Immunologie Clinique et Allergologie, Hôpital Central, 29 Avenue de Lattre de Tassigny, 54035 Nancy Cedex, France. E-mail: g.kanny@chu-nancy.fr.
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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	Ornodazole, piperaccillin
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, hydroxizine, 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.