

Dear Editor

Non-Immediate, Severe Hypersensitivity Reaction to Iopamidol with Cross Reactivity to Different Radiocontrast Agents

Iodinated contrast media (ICMs) are among the most commonly used injectable drugs. It is estimated that more than 75 million administrations are made per year worldwide. ICMs are tri-iodinated benzene derivatives. According to the chemical structure, osmolality, iodine content and ionization in solution they are classified as: i/ high-osmolar ionic monomers (amidotrizoate and ioxitralamate), ii/ low-osmolar ionic dimers (ioxaglate), iii/ low-osmolar non-ionic monomers (iohexol, ioversol, iomeprol, iopentol, iopamidol, iopramide and iobitridol), and iv/ iso-osmolar non-ionic dimers (iodixanol).¹

ICMs are considered safe with most of the reported adverse reactions being mild and self-limited. Hypersensitivity reactions to ICMs can be either immediate (occurring within the 1st hour after the injection) or non-immediate (occurring from 1 hour up to 7 days after the injection). Large observational studies have shown an incidence of mild immediate adverse reactions of 3.8-12.7% and 0.7-3.1% among patients receiving intravenous injections of high-osmolar ionic and low-osmolar non-ionic ICMs respectively, while severe reactions have been reported in 0.1-0.4% and 0.02-0.04%, respectively.^{2,3} On the other hand, the frequency of non-immediate adverse reactions ranged from 0.5 to 23%, reflecting difficulties in confirming causal relationship with ICM injection.⁴ Most ICM-induced non-immediate reactions are manifested by various types of skin eruptions. Well-documented systemic reactions are rarely reported.

We present the case of a 64-year old caucasian male who was submitted to a contrast computerized tomography examination with intravenous iopamidol (IOPAMIRO® 370 mg), a low osmolar non-ionic monomer ICM, for the investigation of a persistent lower abdominal pain, in May 2011. Within 24 hours following the ICM injection, the patient experienced generalized pruritus, while in 48 hours an intensely pruritic erythematous maculopapular rash developed, appearing first on the neck and legs, spreading progressively and becoming generalized. At this time, a general practitioner administered methylprednisolone 250 mg iv. Nevertheless, the rash gradually deteriorated and 6 days after the ICM injection, the patient was referred to us with intense pruritus, generalized maculopapular eruption (Fig. 1A), fever (38°C) and a burning sensation in his eyes. From his medical history, atopy was excluded. He was not taking

any other medication and his drug history was otherwise unremarkable. Two years before, he had received an unknown ICM during computerized tomography uneventfully. Laboratory investigation revealed eosinophilia (960 elements/mm³) and elevated C-reactive protein (16.2 mg/dl) while coagulation parameters and routine chemistry and blood cultures were inconspicuous. A punch biopsy of lesional skin revealed spongiosis, a sparse mixed lymphomonocytic inflammatory infiltrate distributed around the superficial dermal vessels and few fragmented neutrophils (nuclear dust) as shown in Figure 2. The patient was treated with methylprednisolone i.v. (1 mg/kg, tapered by 50% every 2 days for 6 days) and H1-antihistamines (cetirizine, 10 mg bid). Symptoms subsided during the next 4 days while the eruption resolved within 10 days.

Eight weeks after the reaction, according to the recently published European multicenter study,⁵ skin prick and patch tests using undiluted ICM and intradermal tests with 100- and 10-fold dilutions of iopamidol and alternative ICMs (Iobitridol-Xenetix® 300 mg; low osmolar non-ionic monomer and Iodixanol-Visipaque® 300 mg; isosmolar non-ionic dimer) were carried out. All tests performed, including skin prick tests, were positive at the 48-hour reading demonstrating cross reactivity between the tested ICM preparations. Intradermal tests in 1/100, 1/10 dilutions and patch tests (duplicated) at 48-hour reading are shown on Figure 1B, 1C, respectively. Irritant reactions were excluded by using 10 adult controls (5 without and 5 with uneventful previous use of ICMs injection) that underwent the same skin testing without positive reactions in any of them.

In non-immediate reactions to ICMs specific T cells seem to be involved.⁴ This is supported by positive patch and intradermal tests at late readings time points.⁵ In a recent study of 22 patients with delayed hypersensitivity reactions to iodixanol, maculopapular rash in 90%, the delayed skin test results with iodixanol were positive in 11 (50.0%) patients while only 2 of 22 (9%) had both delayed positive IDT and patch test results.⁶ Furthermore, these reactions cannot be prevented by premedication, as it has been repeatedly reported.^{4,6}

In the literature, there are several reports of non-immediate reactions to ICM.⁷ Most of these refer to maculopapular eruptions. Cross-reactivity among the ICM, even across the four groups, is not uncommon in non-immediate reactions.⁸ The present case is interesting in that a severe non immediate systemic hypersensitivity reaction occurred and it was associated with demonstration of cross reactivity between the culprit agent (iopamidol) and ICMs of different classes. In the study of Hasdenteufel *et al.*,⁶ cross reactivity to ionic, nonionic, or both types of ICM was detected in 7 out of 22 cases.

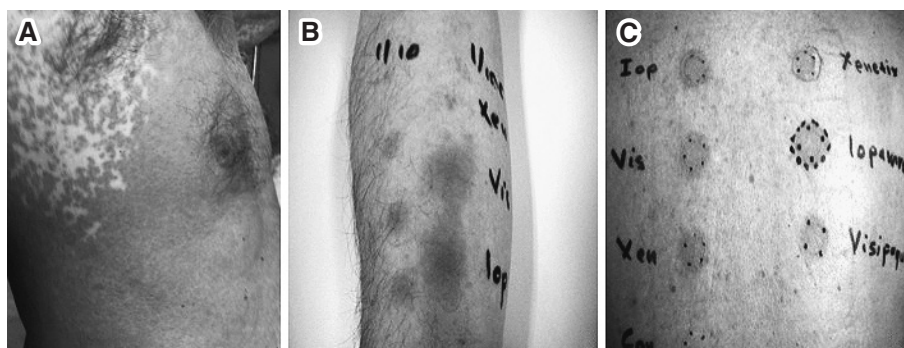


Fig. 1 **A.** Patient's exanthema the 6th day after ICM injection; **B.** the 48-hours positive intradermal tests in 1 : 100 (left) and 1 : 10 (right) ICM dilutions; **C.** the 48-hours positive patch tests in undiluted ICM (duplicated).

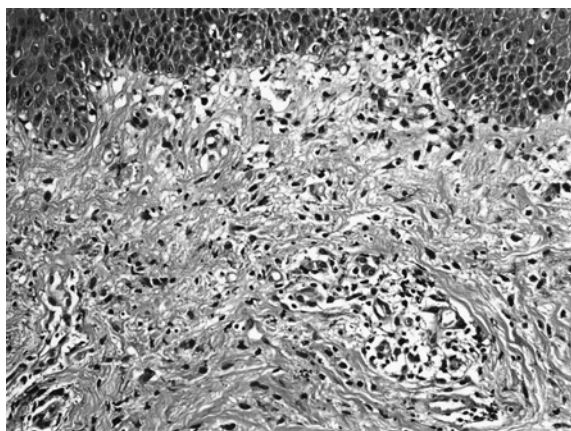


Fig. 2 Histological picture of lesional skin.

As recently shown, particularly in patients with broad skin test positivity to many different RCM, hypersensitivity to iodine seems to be a possible explanation and should be investigated⁹; in our case an oral provocation with Lugol's solution was not carried out due to the severity of the reaction.

Conclusively, although clinicians are often reluctant to perform skin testing in ICMs, especially in non-immediate reactions, skin and patch tests proved to be highly specific^{8,9} when performed properly.⁵ Therefore, they should be performed whenever such reactions occur. Due to the extended use of ICMs in various diagnostic procedures that may necessitate again their use in the future, the allergological diagnostic approach can be the basis for the selection of a safe alternative agent.¹⁰

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