

Clinical Communications

Iodinated contrast media-induced acute generalized exanthematous pustulosis confirmed by delayed skin tests

Aurélien Grandvuillemin, PharmD^a, Cathy Ripert, MD^b, Catherine Sgro, MD^a, and Evelyne Collet, MD^b

Clinical Implication

- Acute generalized exanthematous pustulosis is a rare adverse reaction induced by iodinated contrast media. To our knowledge, we report the largest case series confirmed by skin testing. Another iodinated contrast media with negative test results was safely administered.

TO THE EDITOR:

Although immediate hypersensitivity reactions to iodinated contrast media (ICM) are well recognized, delayed cutaneous reactions (1 hour to 7 days) are much less easily diagnosed. The clinical manifestation usually is moderate, but sometimes serious reactions may occur. To our knowledge, we report the largest series of cutaneous delayed reaction that presented as acute generalized exanthematous pustulosis (AGEP) after ICM administration confirmed by skin testing. Skin tests performed 6 weeks after AGEP included patch tests followed by intradermal tests (IDT).^{1,2} ICMs tested were the same for all patients (ioxaglate, iomeprol, iopamidol, iodixanol, iohexol, iobitridol). Patch tests were conducted with undiluted ICM. Readings were conducted on days 2 and 4. Positive results were considered in accordance with the recommendations of the European Society of Contact Dermatitis.³ IDTs were performed with 10-fold diluted and undiluted ICM, and readings were conducted after 20 minutes and on day 2. Intravenous administration was performed 1 month later by using an alternative ICM that had negative skin tests and was also selected in consultation with the radiologist based on the ICM needed. The first dose injected was 0.5 mL. Two hours later, if no reaction occurred, then 2 mL was injected. The entire dose was administered only for the radiologic examination. All skin tests and intravenous administrations were conducted in a dermatology hospital unit.

REPORT OF CASES

The cases are shown in [Table I](#).

Case 1

A 45-year-old woman received iomeprol for a cerebral computed tomography (CT) and iodixanol for a cerebral arterial embolization the same day. Her main medical history included allergic rhinitis, cigarette smoking, and migraine but no known drug allergy. Three days later, she presented with AGEP confirmed by skin biopsy (subcorneal pustulosis with neutrophils infiltration). Among the tested drugs (iomeprol, iodixanol, Depakine [Sanofi-Aventis] [valproic acid] and Nimotop [Bayer Santé] [nimodipine], which also were suspected based on chronology), only iodixanol patch and IDT

tests were positive. Intravenous administration of iomeprol was tolerated without untoward effects. For this patient, intravenous administration was made the day after negative skin tests results because cerebral CT was urgently indicated.

Case 2

A 26-year-old woman received iomeprol for a cerebral CT for headache. Her main medical history included asthma, tobacco use, and migraine but no known drug allergy. The following day, she developed AGEP, confirmed by skin biopsy. Results of patch and IDT tests were positive for iomeprol. A moderate flexural erythema was observed 6 hours after skin testing. Intravenous administration of iodixanol was tolerated without untoward effects.

Case 3

A 79-year-old woman received iobitridol for a fistulography. Her main medical history included osteoarthritis, primary amyloidosis, and tramadol-induced urticaria. Two days later, she experienced AGEP, confirmed by skin biopsy. Patch and IDT tests were positive for iobitridol. Intravenous administration of iodixanol was tolerated without untoward effects.

Case 4

A 24-year-old man received iomeprol for a cerebral CT and iodixanol for an arteriography the same day in the context of an aneurysm rupture. He had no relevant medical history and no known allergy. He presented with AGEP 24 hours later, confirmed by skin biopsy. Patch and IDT test results were positive for iodixanol. Intravenous administration of iobitridol was tolerated without untoward effects.

DISCUSSION

We report 4 cases of AGEP after ICM administration. In these cases, patch tests were always positive for the suspected ICM as well as delayed IDT (10-fold diluted and undiluted). One patient experienced a moderate relapse after skin testing. When considering the risk of relapse with undiluted delayed IDTs, 10-fold dilution should be considered, as recommended by the European Network of Drug Allergy.² Reintroduction was safe with another ICM, which had negative skin test results. AGEP is a rare skin eruption (1-5 patients per million per year), which usually begins 24 to 48 hours after drug exposure, disseminates quickly, and resolves, after discontinuation of the causative drug, over a period of up to 15 days.^{4,5} There is a predominance in women.⁴

Eleven cases of AGEP induced by ICM were found in the literature.⁵⁻⁸ Two publications mentioned skin tests.^{2,9} Among pustulosis induced by ICM recorded in the French Pharmacovigilance Database, 22 cases of AGEP were found. Six of them (including our 4 cases) were confirmed by skin tests. Skin testing may be useful in confirming the association between severe cutaneous adverse drug reaction, including AGEP, and the culprit drugs. A recent multicenter study had positive patch tests for 58% of patients with AGEP.⁹ In nonimmediate reactions induced by ICM, both delayed IDT and patch tests are recommended to enhance test sensitivity.² For tests conducted within the time period from 2 to 6 months after the reaction, up

TABLE I. Patients and tests details

Case no.	Sex	Age (y)	ICM	Time to onset (d)	Other suspected drugs	Patch tests	Intradermal tests	ICM intravenously administered
1	F	45	Iodixanol	3	Nimodipine, valproic acid, iomeprol, heparin sodium	Iodixanol, +; ioxaglate, -; iomeprol, -; iopamidol, -; iohexol, -; iobitridol, -; nimodipine, -; valproic acid, -; iomeprol, -; heparin sodium, -	Iodixanol, +; ioxaglate, -; iomeprol, -; iopamidol, -; iohexol, -; iobitridol, -; nimodipine, -; valproic acid, -; iomeprol, -	Iomeprol, -
2	F	26	Iomeprol	1	Methocarbamol, paracetamol/tramadol	Iomeprol, +; iodixanol, -; ioxaglate, -; iopamidol, -; iohexol, -; iobitridol, -; methocarbamol, -; paracetamol, -; tramadol, -	Iomeprol, +; iodixanol, -; ioxaglate, -; iopamidol, -; iohexol, -; iobitridol, -	Iodixanol, -
3	F	79	Iobitridol	2	Pentoxifylline	Iobitridol, doubtful; iomeprol, -; iodixanol, -; ioxaglate, -; iopamidol, -; iohexol, -; pentoxifylline, -	Iobitridol, +; iomeprol, -; iodixanol, -; ioxaglate, -; iopamidol, -; iohexol, -; pentoxifylline, -	Iodixanol, -
4	M	24	Iodixanol	1	Nimodipine, levetiracetam, iomeprol	Iodixanol, +; ioxaglate, -; iomeprol, -; iopamidol, -; iohexol, -; iobitridol, -; nimodipine, -; levetiracetam, -	Iodixanol, +; ioxaglate, -; iomeprol, -; iopamidol, -; iohexol, -; iobitridol, -; nimodipine, -; levetiracetam, -	Iobitridol, -

+, Test result was considered positive; -, test result was considered negative or intravenous administration with no reaction.

to 47% positive skin tests have been reported for nonimmediate reactions, for which cross reactivity was more common than for immediate reactions.² ICM should be added to the list of agents that cause AGEF, and skin testing should be recommended to identify the causative agent and to provide a safe alternative ICM.

^aRegional Pharmacovigilance Centre, University Hospital, Dijon, France

^bDepartment of Dermatology, University Hospital, Dijon, France

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication May 23, 2014; revised July 15, 2014; accepted for publication July 24, 2014.

Available online ■ ■

Corresponding author: Aurélie Grandvillumin, PharmD, Centre de Pharmacovigilance de Bourgogne, 14 rue P. Gaffarel, 21079 Dijon, Cedex, France. E-mail: aurelie.grandvillumin@chu-dijon.fr.

2213-2198

© 2014 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2014.07.015>

REFERENCES

- Vernassiere C, Trechot P, Commun N, Schmutz JL, Barbaud A. Low negative predictive value of skin tests in investigating delayed reactions to radio-contrast media. *Contact Dermatitis* 2004;50:359-66.
- Brockow K, Romano A, Aberer W, Bircher AJ, Barbaud A, Bonadonna P, et al. Skin testing in patients with hypersensitivity reactions to iodinated contrast media: a European multicenter study. *Allergy* 2009;64:234-41.
- Barbaud A, Gonçalo M, Bruynzeel D, Bircher A. European Society of Contact Dermatitis. Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. *Contact Dermatitis* 2001;45:321-8.
- Fernando SJ. Acute generalized exanthematous pustulosis. *Australas J Dermatol* 2012;53:87-92.
- Paquet P, Vandenbossche G, Nikkels AF, Henry F, Perard GE. Case of the month. Acute generalized exanthematous pustulosis due to an iodinated contrast radiodiagnostic agent [in French, with English abstract]. *Rev Med Liège* 2009;64:601-5.
- Poliak N, Elias M, Cianferoni A, Treat J. Acute generalized exanthematous pustulosis: the first pediatric case caused by a contrast agent. *Ann Allergy Asthma Immunol* 2010;105:242-3.
- Kim SJ, Lee T, Lee YS, Bae YJ, Cho YS, Moon HB, et al. Acute generalized exanthematous pustulosis caused by radiocontrast media. *Ann Allergy Asthma Immunol* 2010;105:492-3.
- Bavbek S, Sözcü ZC, Aydın O, Özdemir SK, Gül U, Heper AO. First case report of acute generalized exanthematous pustulosis due to intravenous iopromide. *J Invest Allergol Clin Immunol* 2014;24:66-7.
- Barbaud A, Collet E, Milpied B, Assier H, Staumont D, Avenel-Audran M, et al. A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions. *Br J Dermatol* 2013;168:555-62.