

A delayed reaction to the magnetic resonance imaging contrast agent gadobutrol



Hiroshi Nagai, MD, PhD, and Chikako Nishigori, MD, PhD

Clinical Implications

- This is the first report of a delayed hypersensitivity reaction to a gadolinium-based magnetic resonance imaging contrast agent. Patch testing might be useful to confirm the diagnosis and to study potential cross-reactivity to other gadolinium-based magnetic resonance imaging contrast agents.

TO THE EDITOR:

Gadolinium-based magnetic resonance imaging (MRI) contrast agents (GBCA) are used worldwide, as are iodine-based computed tomography contrast agents (IBCA). Adverse reactions to contrast agents are categorized into 2 types, immediate and delayed, according to the timing of the reaction. Delayed reactions to IBCA are not uncommon, but those to GBCA are previously unreported. We present a case of a delayed reaction to the GBCA gadobutrol.

In May 2016, a 62-year-old woman with early stage lung cancer presented with extensive erythematous skin eruptions. Two days previously, she had received 7.5 mL of 1.0 M gadobutrol intravenously for a preoperative chest MRI examination. The eruptions appeared on her abdomen 4 to 5 hours after the administration of gadobutrol, and then gradually spread to almost her entire body. Physical examination revealed an erythematous maculopapular rash on her face, trunk, and extremities (Figure 1). Her mucous membranes (mouth and eyes) were normal on examination, but she stated that her eyes felt itchy. In view of the clinical course and findings, we suspected a delayed adverse reaction to gadobutrol. Histological examination of a skin biopsy specimen revealed liquefaction degeneration at the epidermal-dermal junction and a perivascular infiltrate of lymphocytes in the upper dermis. Complete blood count and biochemical blood test results were normal. Because the lesions were spreading, we treated her with low dose (10 mg/day) oral prednisolone for 4 days. Thereafter, the lesions stopped spreading and gradually disappeared.

Our literature search found no reports of delayed adverse skin reactions to GBCA.¹ In fact, the European Society of Urogenital Radiology Guidelines on Contrast Media (version 9.0)² state that “late skin reactions of the type which occur after iodine-based contrast media have not been described after gadolinium-based and ultrasound contrast media.” Therefore, we tried to clarify whether gadobutrol had actually caused the reaction. The result of the lymphocyte transformation test (to gadobutrol using the patient’s peripheral blood lymphocytes), performed 21 days after the development of the skin reaction, was negative. Twenty-nine days after developing the skin reaction, the patient underwent



FIGURE 1. Maculopapular erythematous rash on the back.

patch testing with gadobutrol (as is), gadobutrol (diluted 1/10), and 0.9% NaCl solution. The test materials were applied to the outside of right upper arm and left for 2 days under occlusion. A positive reaction (1+) according to the International Contact Dermatitis Research Group scoring system³ was observed at the gadobutrol application site (Figure 2). We could not conduct patch testing in exposed controls who did not experience adverse reactions to gadobutrol on ethical grounds. However, a previous report showed that patch testing with undiluted gadobutrol did not show any reaction 48 hours and 72 hours after application in a patient with a fixed drug eruption caused by IBCA.⁴ On the basis of the clinical course and the skin biopsy and patch testing results, we made the diagnosis of a delayed (type IV) allergy to gadobutrol.

The patient had received GBCA three times before the last administration of gadobutrol: 5 mL of gadobutrol, 7.5 mL of gadobutrol, and 15 mL of meglumine gadoterate were administered 24 days, 8 days, and 7 days before the last administration, respectively. We suspected that the patient was sensitized by the gadobutrol administered 8 days before, but wanted to rule out the possibility of sensitization by meglumine gadoterate, because cross-reactivity to several iodinated contrast media has been reported with delayed reactions.⁴ In addition, the patient hoped to

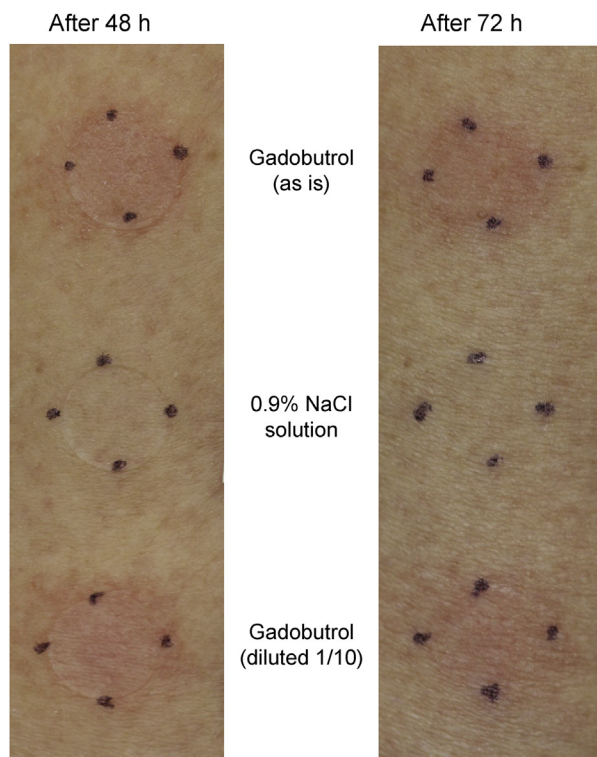


FIGURE 2. After both 48 and 72 hours, the patch test showed a positive reaction at the site to which gadobutrol was applied. The 1/10 dilution was made with 0.9% NaCl solution.

know which GBCA would be available for future use. Therefore, with the patient's consent, we reconducted patch testing using several commonly used GBCA undiluted: gadobutrol and gadoteridol (nonionic macrocyclics), meglumine gadoterate (ionic macrocyclic), gadodiamide hydrate (nonionic linear), and meglumine gadopentetate (ionic linear). Two days later, only gadobutrol showed a positive reaction. These results indicate that the patient became sensitized to gadobutrol and suggest that, except for gadobutrol, other GBCA should be safe for use.

Adverse reactions to contrast media are categorized into 2 types according to the timing of the reaction, immediate and delayed. Immediate and delayed reactions are defined as those that occur within 1 hour, and 1 hour to 1 week after injection of contrast media, respectively. Immediate reactions are either allergy-like hypersensitivity reactions or chemotoxic responses. Symptoms include urticaria, itching, facial/laryngeal edema,

vomiting, and shock. These reactions occur after administration of IBCA and GBCA, but the incidence is higher with the use of IBCA.^{1,2} Delayed reactions to IBCA are characterized by skin reactions similar to other drug-induced eruptions (maculopapular rashes, erythema, swelling, and pruritus)² and are shown to be T-cell mediated.⁵ The reported incidence is 2% to 5%.⁵ Patch and delayed-reading intradermal tests are useful to confirm a delayed reaction to IBCA and to study cross-reactivity to other IBCA.⁵ However, there is currently no information supporting the usefulness of these skin tests for delayed reactions to GBCA. Considering that there are no previous reports of delayed reactions to GBCA, it seems that T-cell sensitization to GBCA is rare. In fact, in preclinical studies, gadobutrol did not demonstrate any contact-sensitizing or other immune-modulating properties.⁶

In conclusion, this case report highlights that T-cell-mediated delayed reactions to GBCA, although rare, can occur. Further, it provides the first data suggesting that patch testing may be useful to confirm the diagnosis and to study potential cross-reactivity to other GBCA.

Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine, Kobe, Japan

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Corresponding author: Hiroshi Nagai, MD, PhD, Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan. E-mail: hnagai@med.kobe-u.ac.jp.

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