Delayed Reaction to Gadobutrol in a Nurse With Myocarditis After SARS-Cov-2 Infection

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J Investig Allergol Clin Immunol 2021; Vol. 31(4): 358-359
doi: 10.18176/jiaci.0706

Key words: Delayed exanthema. Gadobutrol. Cross-reactivity.

Palabras clave: Exantema retardado. Gadobutrol. Reactividad cruzada.

Gadolinium-based contrast agents (GBCAs) are used to diagnose inflammation, tumors, and other tissue disorders. They are classified according to their chemical structure (macrocyclic or linear) and properties (ionic or nonionic). Adverse reactions are uncommon, with prevalence ranging between 0.066% and 1.47% and nausea and vomiting being the most frequently reported [1]. Adverse reactions to contrast media are categorized into 2 types according to whether onset is immediate or delayed. Immediate reactions occur within 1 hour, and delayed reactions occur 1 hour to 1 week after the injection of the contrast medium [2]. Immediate hypersensitivity reactions are infrequent and mostly mild, with urticaria being the most common (incidence of 0.07% in adults and 0.04% in children) [3]. Anaphylaxis occurs in 0.01% of cases [4]. Delayed hypersensitivity reactions with GBCAs are very infrequent.

We report the case of a delayed reaction to gadobutrol during a study of cardiac sequelae after COVID-19 infection.

A 49-year-old nurse was diagnosed with mild COVID-19 infection in April 2020. In June, she volunteered to participate in a cardiac sequelae protocol. After signing the informed consent document, she underwent cardiac magnetic resonance imaging (MRI) with gadobutrol. Twenty-four hours later, she developed mild itching and a widespread erythematous skin eruption. The eruption affected the abdomen and gradually spread to her back. Physical examination revealed an erythematous maculopapular rash on the abdomen, back, and neck without blistering or excoriation (Figure). No mucous lesions were observed. The patient was treated with topical methylprednisolone and oral antihistamines, and the exanthema gradually disappeared after 4 days. She had no history of atopy, adverse drug reactions, or food allergy and had not previously received GBCAs.

An allergy study was performed 1 month after she developed the skin reaction. Patch tests (PTs) with 48- and 96-hour readings and intradermal tests (IDTs) with 6- and 48-hour readings were performed. Reagents included gadobutrol (Gadovist, Bayer), gadoxetate disodium (Primovist, Bayer), and gadoterate meglumine (Dotarem, Guerbet). The tests were based on undiluted GBCAs for PTs and 1:10 dilutions for IDTs [3,5]. The results of both were negative. The MRI revealed myocarditis.

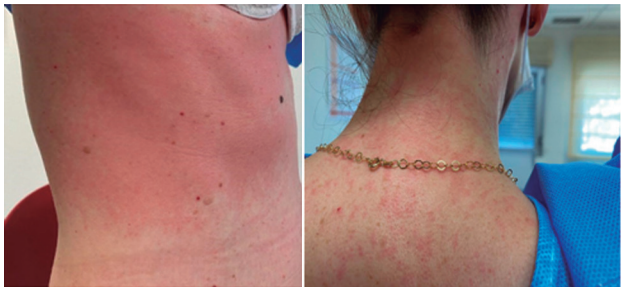

Figure. Maculopapular erythematous rash on the patient's back and neck.

Given the possible need for future MRI scans, the fact that the skin reaction had not been severe, and the uncertain diagnosis, the patient gave her written informed consent to undergo a drug provocation test (DPT) with gadobutrol.

The DPT was performed up to a dose suitable for diagnosis in 2 days, with 1 week of delay.

On the first day, a dose of 1209.44 mg of gadobutrol was administered and well tolerated. One week later, a dose of 4535.4 mg was administered. Fifteen hours after the challenge, the patient developed an itchy erythematous rash on the abdomen, neck, arms, and legs, accompanied by a burning sensation. A single oral dose of 40 mg of methylprednisolone was administered, and topical methylprednisolone was recommended. The exanthema disappeared in 3 days. The patient subsequently agreed to undergo DPT with gadoxetate disodium (linear). Again, a 2-step protocol was used (453.58 mg of gadoxetate disodium on the first day and 1360.73 mg 1 week later). The patient tolerated a full dose of gadoxetate disodium.

We report a case of delayed exanthema with gadobutrol (macrocyclic) with tolerance to gadoxetate disodium (linear). Delayed reactions to GBCAs are extraordinarily infrequent, with only 3 cases described to date, all of them due to gadobutrol [2,6,7]. One case [7] involved acute generalized exanthematous pustulosis (AGEP) due to gadobutrol, with PTs yielding positive results to gadobutrol on days 2 and 4 and negative results to gadoterate meglumine. DPTs were not performed. Another case [2] involved an erythematous maculopapular rash following administration of gadobutrol. PTs were performed with gadobutrol, gadoteridol, and gadoterate meglumine (all macrocyclic), as well as gadodiamide and gadopentetate meglumine (both linear), with positive results reported only to gadobutrol. As in the previous case, DPTs were not performed. The third case [6] was a severe delayed reaction with cutaneous and cardiac symptoms. Neither PTs nor DPTs were performed. In our case report, STs were negative. Notwithstanding, we present the first case of a delayed reaction after administration of gadobutrol that was assessed based on a complete allergology study, including

DPTs, to confirm the diagnosis and offer a safe alternative for subsequent administration of GBCAs.

Cross-reactivity between GBCAs seems to appear in immediate reactions, although it has not been adequately addressed [1,3,4,8,9]. In delayed reactions, it is entirely unknown. In the case we report, the DPT was positive with a macrocyclic agent, and the patient tolerated a linear agent. Similar findings have been reported in immediate reactions, where most patients sensitized to macrocyclic agents tolerate linear agents [10].

In the case of delayed hypersensitivity reactions in a patient who requires a GBCA, we advise performing a DPT with a GBCA other than that involved in the reaction, preferably one with a different molecular structure, provided that the results of skin testing are negative.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Manuscript received March 24, 2021; accepted for publication May 10, 2021.

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