

Delayed Reaction to Gadobutrol in a Nurse with Myocarditis After SARS-CoV2 Infection

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Gadolinium-based contrast agents (GBCAs) are used to diagnose inflammation, tumours, or other tissue disorders. GBCAs are classified according to chemical structure (macrocyclic or linear) and properties (ionic or non-ionic). Adverse reactions are uncommon, with prevalence ranging between 0.066% and 1.47%, nausea and vomiting the most common[1]. Adverse reactions to contrast media are categorized into two types according to the reaction's timing, immediate and delayed. Immediate reactions occur within 1 hour, and delayed reactions occur 1 hour to 1 week after the injection of the contrast media[2]. Immediate hypersensitivity reactions are infrequent and mostly mild, being urticaria the most commonly described, with an 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.

Herein, we report a delayed reaction to gadobutrol during a study of cardiac sequela after COVID-19 infection.

A 49-year-old nurse was diagnosed with a mild COVID-19 infection in April 2020. In June, she volunteered to participate in a protocol of cardiac sequelae. After writing the informed consent, she underwent a cardiac MRI with gadobutrol. Twenty-four hours later, she presented a mild itching, widespread erythematous skin eruption. The eruption appeared on 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 1*). No mucous lesions were observed. After treatment with topical methylprednisolone and oral antihistamines, the exanthema gradually disappeared in four days. She had no history of atopy, adverse drug reactions, or food allergy. She had not previously received GBCAs.

One month after developing the skin reaction, an allergy study was performed. Patch tests (PTs) with 48 and 96 hours reading and intradermal tests (IDTs) with 6 and 48 hours reading were performed. Reagents included gadobutrol (Gadovist® Bayer, Barcelona, Spain); gadoxetate disodium (Primovist® Bayer, Barcelona, Spain); and gadoterate meglumine (Dotarem®, Guerbet, France), using undiluted GBCAs for PTs and 1:10 dilutions for IDTs[3,5], being both negative. Concerning the result of the MRI, she was diagnosed with myocarditis.

Given the possible need for future MRI scans, the fact that the skin reaction had not been severe, and the diagnosis's uncertainty, a drug provocation test (DPT) with gadobutrol was proposed to the patient. She signed the informed consent.

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

On the first day, a dose of 1,209.44 mg of gadobutrol was administered, with good tolerance. One week later, a dose of 4,535.4 mg of gadobutrol was administered. Fifteen hours after the challenge, she presented an itchy erythematous rash in the abdomen, neck, arms, legs, with a burning sensation. A single oral dose of 40 milligrams of methylprednisolone was administered. Also, topical methylprednisolone was recommended. The exanthema disappeared in three days. Therefore, a DPT with gadoxetate disodium (linear) was proposed, and the patient accepted it. Again, a two-step protocol was used (453,58 mg of gadoxetate disodium on the first day and 1360,73 mg one week later). The patient tolerated a full dose of gadoxetate disodium.

We present a case report of a delayed exanthema with gadobutrol (macrocylic) with tolerance to gadoxetate disodium (linear). Delayed reactions to GBCAs are extraordinarily infrequent, with only three cases described so far, all of them due to gadobutrol [2,6,7] One of the them [7] was an acute generalized exanthematous pustulosis (AGEP) due to gadobutrol, with PTs being positive with gadobutrol on day 2 and 4 and negative results with gadoterate meglumine. DPTs were not performed. Another reported case [2] was an erythematous maculopapular rash following

gadobutrol administration. PTs were performed with gadobutrol, gadoteridol and gadoterate meglumine (all macrocyclic), gadodiamide, and gadopentetate meglumine (both linear), showing positivity only to gadobutrol. Again, no DPTs were performed. The third case [6] was a delayed severe reaction with cutaneous and cardiac symptoms. PTs or DPTs were not performed. In our case report, STs were negative. Notwithstanding, we present the first case of a delayed reaction after gadobutrol administration with a complete allergy study performed, including DPTs, to confirm the diagnosis and offer a safe alternative for ulterior GBCA administration.

Cross-reactivity among GBCAs seems to exist in immediate reactions, although it has not been adequately addressed [1,3,4,8,9]. In delayed reactions, it is entirely unknown. In our case report, the patient had a positive DPT with a macrocyclic agent and tolerated a linear agent. That has been described in immediate reactions, where most patients sensitized to macrocyclic agents do tolerate linear agents [10].

We suggest that in the case of delayed hypersensitivity reactions, in which a new administration of GBCA is required, it would be advisable to perform a DPT with an alternative GBCA to that involved in the reaction, preferably with a different molecular structure, provided that STs were negative.

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Figure 1. Maculopapular erythematous rash on the back and neck.

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