

Nonimmediate Maculopapular Erythema Induced by a Gadolinium-Based Contrast Agent

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Gadolinium-based contrast agents (GBCAs) are used to enhance tissue contrast during magnetic resonance imaging (MRI). They can be classified according to ionicity as ionic or nonionic, or according to their molecular structure as macrocyclic or linear. GBCAs are considered safer than iodinated contrast media (ICM), less frequently eliciting immediate hypersensitivity reactions (IHS) (<1 hour after exposure). On the other hand, nonimmediate hypersensitivity reactions (NIHS, >1 hour after exposure) to ICM are well known and described, although not for GBCAs.

We recently published a retrospective analysis of 132 consecutive patients assessed for suspected hypersensitivity to GBCA in our unit [1]. Of the 132 patients tested, 22 (16.7%) had a history of NIHS, but only 1 had positive skin test results confirming an NIHS to GBCAs. We report the case of a patient who experienced GBCA-induced maculopapular exanthema (MPE). The patient gave his consent for publication of his case.

An otherwise healthy 72-year-old man underwent surgery for spondylolisthesis (arthrodesis). Nine months later, a second procedure was performed to remove an osteosynthesis plate. After surgery, the patient developed fever. Blood culture was positive for *Staphylococcus capitis*, and the infection was treated with ofloxacin and rifampicin for 1 month. Three weeks after surgery, a first lumbar MRI with injection of an unknown GBCA revealed spondylodiscitis. Antibiotic therapy was subsequently switched to vancomycin and rifampicin. Five weeks later, given the persistence of fever despite antibiotic therapy, a second MRI was performed with gadobutrol, followed by a computed tomography scan with iopromide 3 days later. On day 8 after this second MRI, the patient developed febrile macular exanthema on the trunk and lower limbs. This was nonpruritic and associated with purpuric lesions on the lower limbs. The patient was

admitted to hospital. Vancomycin and rifampicin were stopped immediately (ie, day 43 after initiation of vancomycin and day 64 after initiation of rifampicin). Paracetamol was maintained as needed.

The laboratory work-up revealed maximum blood eosinophilia at 430/mm³ on day 8 after the onset of the eruption, as well as hepatic cytolysis (AST and ALT at 4 ULN), although kidney function remained close to the upper limit (maximum blood creatinine, 110 µmol/L). The results of polymerase chain reaction assay were negative for human herpesvirus 6, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, varicella zoster virus, and parvovirus B19, as were those of serology testing for hepatitis A virus (HAV), HBV, HCV, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*. Antinuclear antibodies and repeated blood cultures were also negative. The skin biopsy revealed vacuolar alterations at the dermoepidermal junction, inflammation in the epidermis and superficial dermis, with lymphocytic and histiocytic infiltrate and pericapillaritis. These findings were compatible with drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.

The cutaneous reaction lasted 8–10 days and resolved with desquamation and no scarring. Despite the delay of 8 days between the exposure and the onset of the reaction, DRESS syndrome was included in the differential diagnosis, although it was ruled out by the RegiScar score [2], which was 2. The clinical presentation was therefore indicative of severe MPE.

The allergy work-up was carried out according to the recommendations of ENDA-EAACI [3]. Skin tests were performed using the prick test followed by intradermal tests (IDT) for vancomycin (maximum, 0.1 mg/mL) and rifampicin (maximum, 6 mg/mL), as well as for undiluted ICM including amidotrizoate, ioxitalamate, iopamidol, iohexol, ioversol, iopromide, iomeprol, iobitridol, and iodixanol. The results were negative at the immediate and delayed readings. Six GBCAs were tested using prick test and IDT up to the undiluted product, as follows: gadoteric acid, gadobutrol, gadopentetate dimeglumine, gadobenic acid, gadodiamide, and gadoteridol. Skin tests were negative at the immediate and delayed readings, except for IDT with gadoteridol, whose delayed reading was positive with the undiluted GBCA. The skin test with gadoteridol was repeated to confirm the positive result. No drug provocation tests (DPTs) were performed because of the possible severe drug-induced reaction and because there was no need for the patient to receive those agents again in the near future. However, the timing of the reaction and the fact that skin tests were negative for every drug except gadoteridol leads us to consider it the cause of the severe MPE. Gadoteridol was therefore contraindicated, and all the other GBCAs were permitted for future use. To our knowledge, the patient did not subsequently undergo MRI. The second MRI, 8 days before the MPE, was allegedly performed with gadobutrol, although we think that the patient actually received gadoteridol. Mismatches of this type have already been reported in our series [1], probably because of recall bias or because patients were misinformed at the time of their reaction.

We report a case of severe MPE induced by gadoteridol. We first included DRESS in the differential diagnosis despite

the short delay of 8 days between exposure and onset of the reaction. Soria et al [4] previously reported that DRESS syndrome induced by ICM can happen with a delay of 7 days or less [4]. It is currently unknown whether this is also the case for GBCAs.

Nonimmediate reactions to GBCA have rarely been reported, and none were confirmed by IDT. In 2017, a case of NIHS to gadobutrol was described in a 62-year-old woman who presented with extensive erythematous skin eruptions 2 days after injection of a GBCA [5]. Patch testing with gadobutrol yielded a positive reaction (1+) and confirmed the diagnosis [6]. In 2018, another case report of an NIHS to gadobutrol was published [7]. However, the history was poorly convincing in terms of allergy. Indeed, the patient received several drugs in addition to gadobutrol, and no allergy work-up was performed. The same year, a case of acute generalized exanthematous pustulosis following injection of a GBCA was also described [8]. In this case, the GBCA was unknown. Patch testing with undiluted gadoteric acid and gadobutrol revealed positive reactions to gadobutrol only. When patch test results are positive, IDT is not necessary. Recently, a case of MPE with gadoteric acid was mentioned in a study about DPT with a low-dose GBCA [9]. Despite negative skin test results, the patient experienced MPE again after a DPT. The present case is therefore the first report of a delayed reaction to a GBCA with positive IDT results. Although GBCAs are not frequently reported as the culprit in NIHS, they should be included among the possible causes and not overlooked. As described in this case and elsewhere [1], mismatches between the GBCA reported and that involved are possible. Exploring patients with several GBCAs could avoid underdiagnosing hypersensitivity to these agents.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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