

## Non-Immediate Maculopapular Erythema To Gadolinium-Based Contrast Agent

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

We recently published a retrospective analysis of 132 consecutive patients investigated for suspicion of GBCA hypersensitivity (HS) in our Unit [1]. Among the 132 tested patients, 22 (16.7%) had a history of NIHS but only one had positive skin tests confirming a NIHS to GBCA.

A 72-year-old man without medical history or regular medication, had surgery for spondylolisthesis consisting of arthrodesis. Nine months later, a second surgery was performed to remove an osteo synthesis plate. After the surgery, the patient presented fever with positive blood cultures for *Staphylococcus capitis* for which treatment with Ofloxacin and Rifampicin was introduced for one month. Three weeks after the surgery, a first lumbar MRI with injection of an unknown GBCA was performed and showed a spondylodiscitis appearance. Following this discovery, a switch of antibiotic therapy to Vancomycin and Rifampicin was carried out. Five weeks later, given the persistence of fever despite antibiotherapy, a second MRI with Gadovist™ (Gadobutrol) was performed, followed by a CT-scan with Iopromide three days later. On day 8 after this second MRI, the patient presented a febrile macular exanthema on the trunk and lower limbs, non-pruritic and associated with purpuric lesions of the lower limbs justifying admission to hospital. Vancomycin and Rifampicin were immediately stopped (i.e on day 43 after the

initiation of Vancomycin and on day 64 after the initiation of Rifampicin). Paracetamol taken as needed was maintained.

The biological assessment found a maximum blood eosinophilia at  $430/\text{mm}^3$  on day 8 after the onset of the eruption. Hepatic cytolysis was also found (AST and ALT at 4 ULN) but kidney function remained close to the upper limit (maximal creatinemia:  $110 \mu\text{mol/L}$ ). HHV6, CMV, EBV, HSV, VZV and Parvovirus B19 PCRs were negative, as were serologies for HAV, HBV, HCV, *chlamydia* and *mycoplasma pneumoniae*. Antinuclear antibodies and repeated blood cultures were also negative. The skin biopsy described vacuolar alterations at the dermo-epidermal junction, inflammation in the epidermis and superficial dermis with lymphocytic and histiocytic infiltrate and pericapillaritis, compatible with a drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.

The cutaneous reaction lasted between eight to ten days and ended with desquamation without any scarring. Despite the delay of eight days between the exposure and the onset of the reaction, DRESS was included in the differential diagnosis. Nevertheless, the Regi Scar score [2] was calculated at two and did not allow to retain a diagnosis of DRESS. The clinical presentation was therefore evocative of a severe maculopapular exanthema (MPE).

The allergy work-up was carried out according to the recommendations of ENDA-EAACI [3]. Skin tests were performed with prick test followed by intradermal test (IDT) for Vancomycin (maximum c% 0.1mg/ml) and Rifampicin (maximum c% 6 mg/ml) as well as for undiluted ICM including Amidotrizoate, Ioxitalamate, Iopamidol, Iohexol, Ioversol, Iopromide, Iomeprol, Iobitridol and Iodixanol. These explorations came back negative in immediate and delayed readings. Concerning GBCAs, six were skin tested by prick test and IDT up to undiluted product: Dotarem™ (Gadoteric acid), Gadovist™ (Gadobutrol), Magnevist™ (Gadopentetate dimeglumine), Multihance™ (Gadobenic acid), Omniscan™ (Gadodiamide) and Prohance™ (Gadoteridol). Skin tests were negative in immediate and delayed readings, except for Prohance™ IDT whose delayed reading was positive with the undiluted GBCA. The skin test with Prohance™ was repeated a second time to confirm the positivity. No drug provocation tests

(DPT) were performed because of the possible severe toxidermia 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 ST were performed and came back negative for every drug except Prohance™ allow us to consider it as the culprit for the severe MPE. Prohance™ was therefore contraindicated and all other GBCA were permitted for future use. To our knowledge, the patient did not undergo any MRI afterwards. The second MRI, eight days before the MPE, was allegedly performed with Gadovist™ (Gadobutrol). We think it is likely that the patient received indeed Prohance™ instead. This kind of mismatches have already been reported in our series [1]. This can be explained by a recall bias, or patients can have been misinformed at the time of their reaction.

We reported here a case of severe MPE to Prohance™. We first included DRESS in the differential diagnosis despite the short delay of eight days between the exposition and the onset of the reaction. It was previously described by Soria et al. that DRESS to ICM can happen with a delay of seven days or less [4]. It is currently unknown if it can be the case for GBCA as well.

Non-immediate reactions to GBCA have rarely been reported and none of them 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 two days after GBCA injection [5]. Patch testing with gadobutrol showed a positive reaction (1+) and confirmed the diagnosis [6]. In 2018, another case report of a NIHS to gadobutrol was published [7]. However, the history was poorly convincing from an allergy point of view. Indeed, the patient received several drugs in addition to gadobutrol and no allergy work-up were performed. The same year, a case of acute generalized exanthematous pustulosis (AGEP) following GBCA injection was also described [8]. In this case, the injected GBCA was unknown. Patch testing was performed with undiluted gadoteric acid (Dotarem®) and gadobutrol (Gadovist®) and showed positive reactions to gadobutrol only. When PT results are positive, it is not indicated to perform IDT. Recently, a case of MPE with gadoteric acid was mentioned in a study about DPT with low dose GBCA [9]. Despite negative ST, the patient experienced MPE again after a DPT. Our case is therefore the first report of a delayed reaction to GBCA with positive IDT. Although GBCA are not frequently reported as the

culprit in NIHS, they should be included among the possible causes and should not be overlooked. As described in this case and previously [1], mismatches between the GBCA reported and involved are possible. Exploring patients with several GBCA could avoid underdiagnosing HS to GBCA.

Consent to publication was obtained from the patient.

**Conflicts of interest**

None for this paper.

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## References

- 1-Mankouri F, Gauthier A, Srisuwatchari W, Moutou A, Borushko A, Popa L, et al. Hypersensitivity to gadolinium-based contrast agents: a single-center retrospective analysis over 7 years. *J Allergy Clin Immunol Pract.* 2021;9(4):1746-9.e2
- 2-Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol.* 2007;156(3):609–11.
- 3-Brockow K, Romano A, Aberer W, Bircher AJ, Barbaud A, Bonadonna P, et al. European Network of Drug Allergy and the EAACI interest group on drug hypersensitivity. Skin testing in patients with hypersensitivity reactions to iodinated contrast media - a European multicenter study. *Allergy.* 2009;64(2):234-41.
- 4-Soria A, Bernier C, Veyrac G, Barbaud A, Puymirat E, Milpied B. Drug reaction with eosinophilia and systemic symptoms may occur within 2 weeks of drug exposure: A retrospective study. *J Am Acad Dermatol.* 2020;82(3):606–11.
- 5- Nagai H, Nishigori C. A delayed reaction to the magnetic resonance imaging contrast agent gadobutrol. *J Allergy Clin Immunol Pract.* 2017;5(3):850-1.
- 6-Fonacier L. A practical guide to patch testing. *J Allergy Clin Immunol Pract.* 2015;3:669-75.
- 7-Boehm I, Heverhagen JT. Delayed reaction following gadolinium-based contrast agent application. *Magnetic Resonance Imaging.* 2018;50:10–1.
- 8-Bordel Gómez MT, Martín García C, MeseguerYebra C, ZafraCobo MI, Cardeñoso Álvarez ME, Sánchez Estella J. First case report of acute generalized exanthematouspustulosis (AGEP) caused by gadolinium confirmed by patch testing. *Contact Dermatitis.* 2018;78:166–8.

9-Seta V, Gaouar H, Badaoui A, Francès C, Barbaud A, Soria A. Low-dose provocation and skin tests in patients with hypersensitivity to gadolinium-based contrast agents. *Clin Exp Allergy*.2019;49:724–8.

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