Hidden Dangers of Oral Contrast Media: Delayed Hypersensitivity to Sodium Amidotrizoate and Meglumine Amidotrizoate (Gastrografin)

Pardo-Manrique V[1], Amat-Samaranch V[2], Pascal M[3], Loli-Ausejo D[4,5], Sánchez-Fernández MC[4], Ruano-Zaragoza M[4,5]

[1]*Icesi University, Allergy Unit, Fundación Valle de Lili, Cali, Colombia.*

[2]*Dermatology Department, Hospital Clínic, Barcelona, Spain*

[3]*Immunology Department, Centre de Diagnòstic Biomèdic (CDB), Hospital Clínic Barcelona, Barcelona, Spain*

[4]*Allergy Department, Hospital Clínic, Barcelona, Spain*

[5]*Clinical and Experimental Respiratory Immunoallergy, Institut Investigacions Biomediques August Pi I Sunyer (IDIBAPS), Barcelona, Spain*

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Palabras clave: Alergia retardada a medicamentos. Amidotrizoato de sodio y amidotrizoato de meglumina. Contraste yodado oral. Medios de contraste yodado intravenosos. Reacciones de hipersensibilidad retardada.

Sodium amidotrizoate and meglumine amidotrizoate (SAMA [Gastrografin]) is a common iodinated contrast agent. Intravenous and oral contrast agents are routinely used in cancer patient monitoring. While adverse reactions to intravenous contrast are well-documented, reactions to oral contrast are rare, although serious cases have been reported. These include 2 anaphylactic reactions [1-2] and a case of toxic epidermal necrolysis (TEN) [3]. We present a case of delayed hypersensitivity reaction (DHSR) following oral diluted SAMA and report the results of the allergology study. The study was conducted according to the tenets of the Declaration of Helsinki, good clinical practice, and local regulations. The patient gave her written informed consent for the publication of this clinical case.

A 66-year-old woman with stage IV breast cancer was referred for suspected allergy after administration of iodinated contrast. In August 2023, she underwent a computed tomography (CT) scan with intravenous iohexol; 2 hours later, she developed facial erythema and mild angioedema, followed by a micropapular rash on the upper body and extremities lasting 4 days. Her condition resolved with oral antihistamines, leaving only hyperpigmented macules. Skin tests (prick testing [at a concentration of 1/1] and intradermal testing [at 1/100 and 1/10]) were performed following the Spanish Society of Allergology and Clinical Immunology (SEAIC) protocol [4]. The test results were negative for ioversol, iohexol, and iopramide in both the immediate and the late readings.

In October 2023, the patient tolerated a controlled iohexol exposure test (100 mL). However, in November, during a new CT scan with iohexol, she developed nonpruritic cervical erythema 15 minutes after exposure. This progressed to facial erythema after 3 hours, with no other lesions (Figure-S1). She received cetirizine, and her condition improved in 48-72 hours. Subsequently, in January 2024, during another CT scan with intravenous iohexol and with premedication (administered as a precaution), the patient developed generalized erythema and well-defined erythematous-violaceous annular skin lesions. These were more extensive on the back and were followed by desquamation (Figure-S2). She was treated with antihistamines and oral corticosteroids, and her condition resolved within 4 weeks. To date, neither the patient nor the health professionals who referred her to our department for the iodinated contrast study had told us that, in addition to the intravenous contrast, she had also received oral contrast in all the previous CT scans. The patient reported that, after this last reaction, she developed facial erythema on administration of oral SAMA, prior to receiving iohexol, and confirmed that she had received both contrasts in all previous CT scans.

We performed additional diagnostic studies, including a lymphocyte transformation test, which was negative for iohexol, SAMA, and ioversol. Patch tests performed according to the recommendations of the European Academy of Allergology and Clinical Immunology and the European Network for Drug Allergy [5] with SAMA (undiluted) and iohexol (undiluted) applied to healthy skin and the postinflammatory hyperpigmented macule were negative at 96 hours. Skin prick tests with SAMA following the SEAIC protocol [4] were negative in the immediate reading but positive in the delayed reading (2 hours), with the appearance of a 4-mm papule, associated with pruritus and subsequent local desquamation (Figure).

The results obtained confirmed DHSR to SAMA. Avoidance of SAMA was recommended. Iohexol was permitted, since the patient tolerated it, although it was recommended to limit use of iodinated contrasts (this recommendation was purely precautionary). A follow-up CT scan with iohexol in April 2024 did not induce a reaction.

SAMA (370 mg iodine/mL) is a water-soluble iodinated contrast agent. For abdominal CT scans, 30 mL in 1 L of water or 45 mL in 1.5 L of 3% solution is administered orally up to 1500 mL in total. This isotonic solution is minimally absorbed (3%) in the gastrointestinal tract, with mild adverse effects such as nausea, vomiting, and diarrhea. The prevalence of adverse skin reactions to iodinated contrast agents,

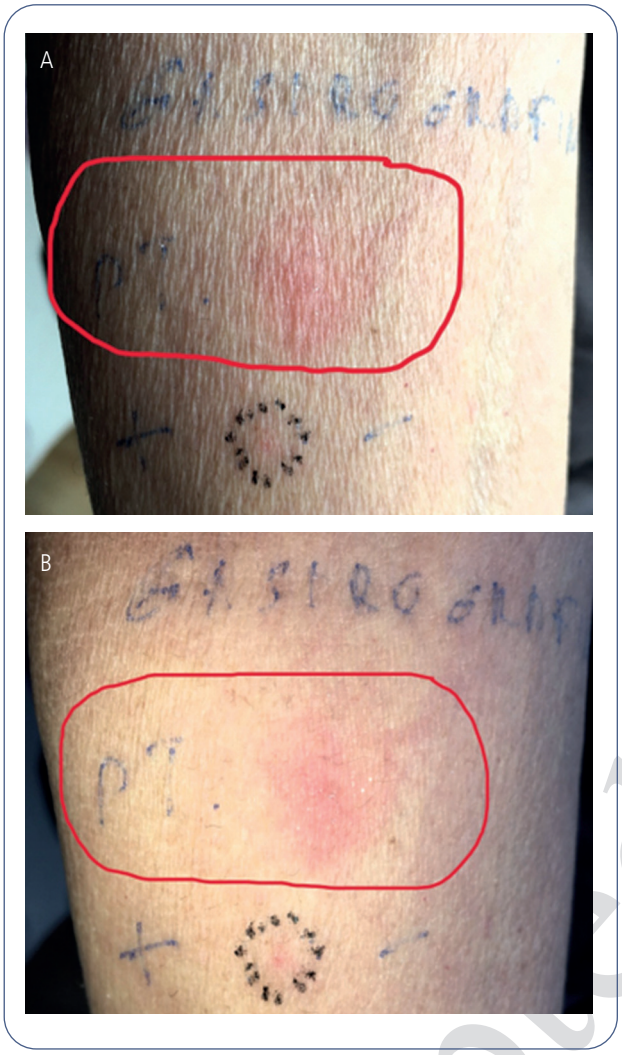

Figure. Positive delayed results of skin prick test with SAMA (A) followed by desquamation (B).

including SAMA, ranges from 1/10 000 to 1/1000. These effects range from urticaria, erythema, and rash to more severe presentations, such as TEN [6].

The prevalence of adverse reactions to nonionic contrast media has increased to between 1% and 3% [7-8]. Immediate and delayed reactions include allergic and nonallergic hypersensitivity, toxic reactions, and reactions unrelated to intravenous contrast media. DHSRs to iodinated contrast agents occur in 0.5%-3% of cases [8], often manifesting as maculopapular rash, although they can also take the form of severe conditions, such as Stevens-Johnson syndrome and TEN. Persistent late-onset urticarial rashes with a generalized distribution are less frequent [8,9].

DHSRs are typically T cell–mediated (type IV), involving $CD4^+$ and $CD8^+$ cells. In this case, the patient's symptoms, coupled with the delayed onset of the rash and positive delayed hypersensitivity in skin tests, strongly suggest a T cell–mediated reaction. Although immediate reactions to contrast media, which are typically IgE-mediated, are more common, the present case falls under the category of nonimmediate hypersensitivity reactions, which have been shown to involve T-cell activation and cytokine release [8].

Several studies have documented both immediate and delayed hypersensitivity reactions to iodinated contrast media, although reports specifically addressing oral contrasts such as SAMA are uncommon. In comparison to previously reported cases, including the one where TEN was associated with SAMA [3], the reaction we report was less severe but still posed a significant clinical challenge. A further 2 cases involved anaphylactic reactions associated with SAMA [1,2]. Most literature in this area focuses on reactions to intravenous contrast media. However, the present case adds to the evidence that oral administration can also elicit serious hypersensitivity responses. Notably, the patient did not exhibit common risk factors for severe delayed reactions, such as preexisting inflammatory bowel disease or a history of multiple contrast exposures, further distinguishing this case from others reported in the literature [1-3].

While a skin biopsy could have provided histological confirmation of the T cell–mediated process, the nonperformance of this test is mitigated by the positive delayed hypersensitivity tests, which revealed clear reactivity to SAMA. Additionally, the resolution of symptoms after avoiding the contrast agent further supports the diagnosis of DHSR in the absence of histopathological evidence.

When assessing a patient affected by DHSR to contrast media, clinicians rarely consider the possibility that contrast media administered via the gastrointestinal route is the culprit, with intravenous contrast media being more commonly thought of. The main complication of oral administration, especially in mentally impaired patients, is aspiration pneumonia [6,10].

Many idiosyncratic reactions to contrast media are not related to the dose or concentration of the agent administered, as a small amount of contrast medium can precipitate a reaction. One of the theories explaining this type of reaction is genetic variability between patients, in whom the contrast medium can be absorbed through epithelial membranes and act as a hapten, thus generating immunological reactivity [3].

The agent responsible in the present case was SAMA, as demonstrated by complete allergology studies that ruled out sensitization to intravenous contrast medium and confirmed tolerance on 2 occasions. Our findings provide valuable knowledge and act as a wake-up call for health professionals caring for patients with hypersensitivity reactions to contrast media. It is essential to actively ask patients whether they had received contrast media orally, as they often only remember and mention intravenous contrast media.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Maria Ruano-Zaragoza
Allergy Department, Hospital Clinic
C. de Villarroel, 170
08036 Barcelona, Spain
E-mail: mruanoz@clinic.cat