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Maculopapular rash due to delayed-type hypersensitivity from ioversol with positive patch tests

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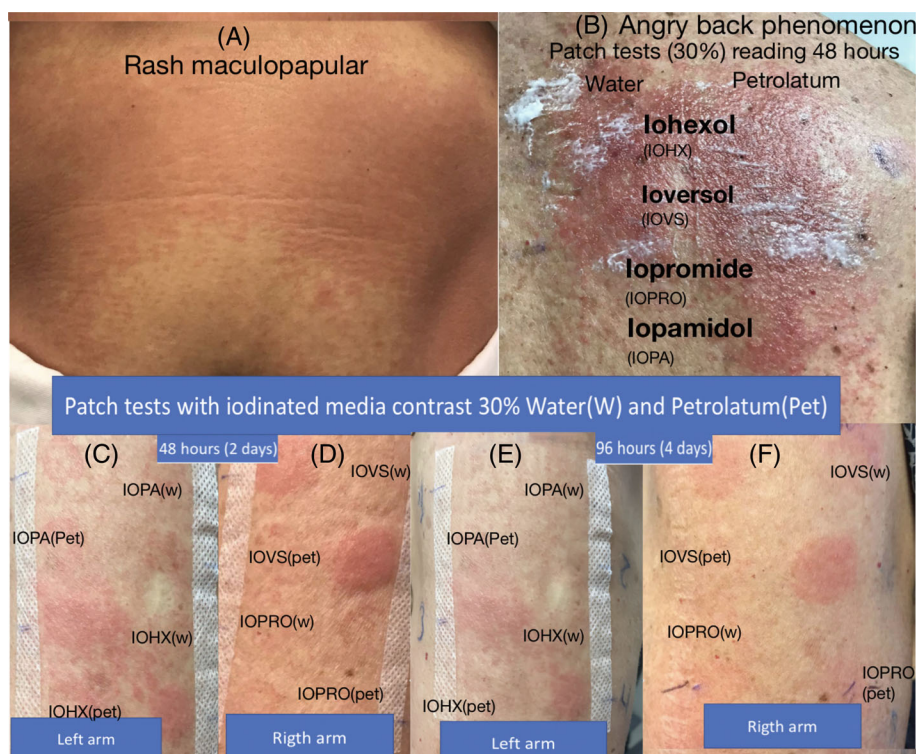
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Non-ionic iodinated contrast media (NICMs) are the preferred option for enhanced Computerized tomography (CT) examination. Adverse reactions to contrast media occur with cutaneous manifestations to fatal, life-threatening complications.¹

Immediate hypersensitivity reactions (IHRs) occur up to 1 h after NICM administration,² mainly if the responses are 'moderate' (in contrast to severe reactions, which may indeed appear within 1H).³ HRs are delayed (DHRs) if they occur more than 1 h to 7 days

FIGURE 1 (A) Micro-maculopapular rash. (B) Difficult to interpret positive patch tests (PT) at the back 'angry back' to non-ionic iodinated media contrasts 30%, pet. and aq. (iohexol, ioversol, iopromide and iopamidol). (C) Re-test PT (reading at 2 days): upper: iopamidol 30% pet. (left) and aq. (right), both erythema (+); below: iohexol 30% (+++), pet. (left) and aq. (right). (D) Re-test PT (reading at 2 days): upper: ioversol 30% pet. +++ (left) and aq. ++ (right); below: iopromide 30%, pet. (left) and aq. (right), both negative. (E) Reading at 4 days: upper: iopamidol 30%, pet. (left) and aq. (right), both negative; below: iohexol 30% (++), pet. (left) and aq. (right). (F) Reading at 4 days: upper: ioversol 30% pet. (left, ++) and aq. (right, +); below: iopromide 30%, pet. (left) and aq. (right), both negative



after NICM administration (most often several hours or sometimes days).²

CASE REPORT

We present a 63-year-old female with a personal history of ovarian carcinoma. Six months ago, she was examined with a contrast-

TABLE 1 Results of patch tests in the patient with non-ionic iodinated contrast media

30% pet. and aq.)	2 Days	3 Days	4 Days
Iopamidol	+	–	–
Iohexol	+++	+++	+++
Iopromida	–	–	–
Ioversol	+++	+++	+++

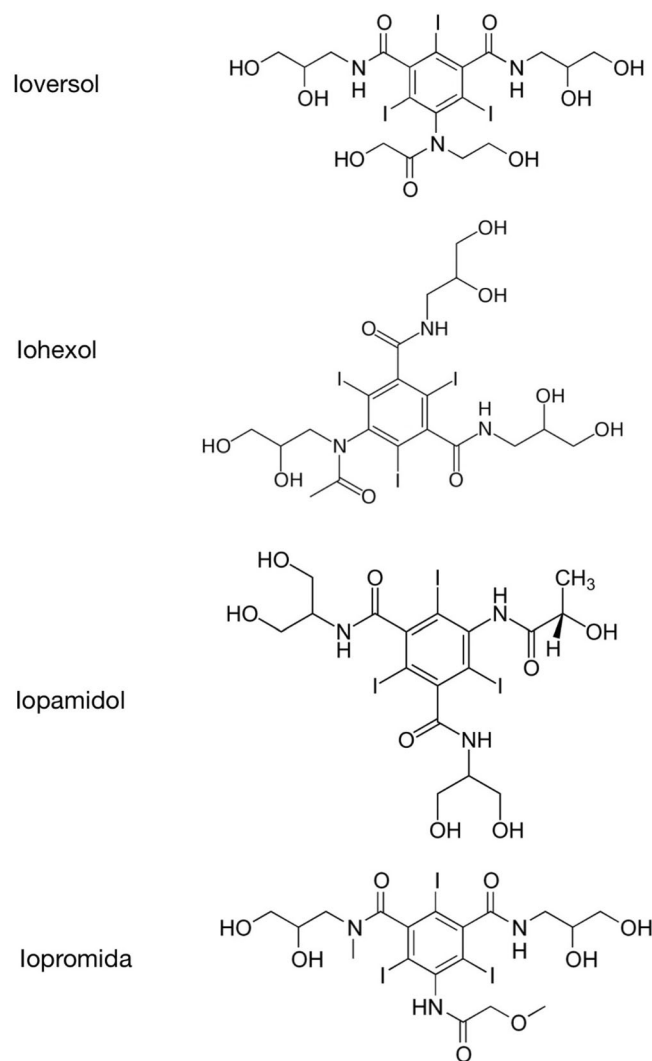


FIGURE 2 The chemical formula of the non-ionic iodinated contrast media studied in the patient (ioversol, iohexol, iopamidol and iopromida)

enhanced CT. Four hours later, after the ioversol injection, an itchy maculopapular rash appeared (Figure 1A), which generalized in less than 24 h. She was treated with corticosteroids (deflazacort 30 mg/day/7 days) and oral antihistamines (bilastine 20 mg/day/15 days). Rash took around 2 weeks to disappear, with slight desquamation.

Three months later, patch tests (PT) were performed: True test (Marti Tor), all negative; as well as PT (using Curatest; Marti Tor) with four NICMs (iopamidol, iohexol, ioversol and iopromida) (both diluted 30% in water and petrolatum), occluded for 2 days, and read on Days 2, 3 and 4. However, as the eight PTs with these NICMs, were placed closely together on the back; it was challenging to read the reactions ('angry back phenomenon') (Figure 1B).

Thereupon, we re-tested (30% pet. and aq.) on the left arm, iopamidol (Figure 1C,E, above) and iohexol (Figure 1C,E, below), and the results were extremely positive reactions (+++) on Days 2, 3 and 4 to iohexol preparations. Erythema (+) to both iopamidol preparations (above) on Day 2 (Figure 1C), but negative to iopamidol on Days 3 and 4 (Figure 1E, above). At the right arm (30% pet. and aq.), we re-tested ioversol (Figures 1D,F, above) and iopromida (Figure 1D,F, below). Iopromida remained entirely negative, but PT with iohexol was positive to both preparations (+++) on Day 2 (Figure 1D), Day 3 and Day 4 (Figure 1F; Table 1).

We performed PT on four control subjects with a history of receiving at least one of the four NICMs tested with a negative result in all controls and readings.

Due to the study results, we recommend iopromida at follow-up CT scans with NICM. As ioversol belongs to the same pharmacological group of the iopromida (monomeric, not ionic. Figure 2), we also recommended treatment with deflazacort (30 mg/day) from 2 days before to 4 days after NICMs are administrated.

DISCUSSION

It is assumed that DHRs are at least as common as IHRs. IHR frequency was 3.8%–12.7% in patients receiving high-osmolar ionic CM and 0.7%–3.1% in low-osmolar NICM. DHR occurred in approximately 0.5%–23% of patients with a significant variation because it is not clear whether symptoms were due to NICM.⁴

Our patient had a DHR as the maculopapular rash began 4 h after administering ioversol, and the PTs were positive for the NICM administered. This patient had a maculopapular rash, which is the manifestation most frequent of DHS due to allergy to NICM.⁴

All NICM tested were in the same group. For this reason, in addition to recommending the patient iopamidol because the PTs were negative, we also recommend premedication. The same is suggested in a recent study.⁴

An 'angry back' phenomenon occurred due to the proximity of the PT with the four NICMs, where ioversol and iohexol caused so severe reactions that no reliable interpretation was possible. Therefore, the four NICMs were re-tested, on separate skin locations, eventually allowing us to identify the NICMs as positive.

In conclusion, we present a pruritic maculopapular rash due to DHR to ioversol with positive PT and cross-reactivity with iohexol.

AUTHOR CONTRIBUTIONS

Alejandro Raúl Gratacós Gómez: Conceptualization; methodology. **Juana Bautista Joyanes Romo:** Investigation. **Jaime Vinicio Meneses Sotomayor:** Writing – original draft. **M. Aranzazu Martín Iglesias:** Investigation. **Alberto Palacios Cañas:** Resources. **Elisa Gómez Torrijos:** Writing – review and editing; supervision.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Delayed-type hypersensitivity reaction to St. John's wort extract confirmed by patch testing

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KEY WORDS: case report, delayed-type hypersensitivity, drug patch testing, St. John's wort

St. John's wort (*Hypericum perforatum*) is a wild flowering plant and its extracts have been used for centuries to treat mental health problems including low mood, depression and anxiety.¹ Side effects and drug interactions are commonly seen, as it is well-known to induce the liver enzyme CYP3A4.² True allergic or hypersensitivity reactions to St. John's wort, are less well-described and rarely reported.^{3,4} Here, we report a novel case of delayed-type hypersensitivity to St. John's wort extract tablets, confirmed by patch testing.

CASE REPORT

A 54-year-old female was referred to the allergy clinic for a suspected adverse drug reaction. She had no history of atopy or other medical

histories. She developed a maculopapular exanthem 24 h after taking oral aspirin and 10 days after commencing St. John's wort extract tablets (334 mg daily). There was no evidence of mucosal involvement or other severe cutaneous adverse reaction features. No other medications were implicated. Blood tests and a skin biopsy were not performed. She immediately stopped both aspirin and St. John's wort following the skin eruption and was treated with oral prednisolone which led to full rash resolution over 4 weeks (with subsequent skin peeling). There was no prior history of dermatitis and no chemical or contact triggers on enquiry. Delayed-type hypersensitivity to either aspirin or St. John's wort extract tablets was suspected given the clinical presentation. Informed consent was obtained from the patient for publication.

In the allergy clinic 4 months later, patch tests were performed using IQ Ultra chambers (Chemotechnique Diagnostics) with St. John's