

LETTER TO THE EDITOR

Immune-mediated drug reaction to indocyanine green: a red light for a green dye

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To the Editor,

We present a rare case of a severe immediate immune-mediated drug reaction to indocyanine green (ICG) in a 68-year-old woman, in which the basophil activation test (BAT) played a pivotal role in establishing the diagnosis and preventing further exposures to the culprit drug.

ICG is a water-soluble, amphiphilic iodized tricarbo-cyanine featuring an excitation peak of ~780 nm and emission around 820 nm. It is used as an intravenous contrast agent in near-infrared fluorescence imaging to evaluate a wide range of cardiovascular, hepatic, neurological and ophthalmological conditions (1).

The patient's medical history was notable for non-allergic asthma, chronic rhinosinusitis without nasal polyposis, irritable bowel syndrome, a previous transient ischemic attack and central retinal artery occlusion of the left eye in 2015, resulting in functional monocular vision. Previous exposures to iodinated contrast media in 2006 and 2021 were uneventful. The patient's medication included pantoprazole, levothyroxine, clopidogrel, co-valsartan, budesonide/formoterol, mometasone nasal spray, bempedoic acid, and latanoprost ophthalmic drops. No previous history of immune-mediated drug reactions or atopy had been documented. She had never previously been exposed to ICG.

ICG was administered in June 2025 as part of the diagnostic evaluation of scleral thickening of the right eye. Immediately after the injection, the patient developed severe anaphylaxis, manifested by diffuse erythema of the face and chest, accompanied by tongue angioedema, and dyspnea, with rapid progression to anaphylactic shock. On assessment, she demonstrated significant hemodynamic compromise, including tachycardia (127 beats/min), profound hypotension (70/40 mmHg), and oxygen desaturation to 93% on room air.

Intramuscular administration of epinephrine (0.5 mg) was performed in the lateral thigh, repeated twice, resulting in a rapid improvement of the symptoms. She also received 1 liter of intravenous fluids and 40 mg methylprednisolone succinate, and was subsequently admitted for observation with cardiorespiratory monitoring, without further complications.

Levels of serum tryptase increased significantly during the acute phase (58.8 $\mu\text{g/L}$), subsequently reducing to 10.6 $\mu\text{g/L}$ after 24 hours. This finding was indicative of mast cell activation, as determined by the consensus formula (2). After 1 month, the baseline value remained persistently elevated (16.3 $\mu\text{g/L}$). Given the severity of the clinical presentation, further investigations were performed for an underlying primary mast cell disorder. These included high-sensitive KIT D816V mutation analysis with digital droplet PCR on peripheral blood, which was negative, and genotyping of TPSAB1 and TPSB2. The latter showed a TPSAB1 duplication matching the baseline tryptase according to Chovanek et al (3). Based on these findings and a REMA score of 0 (4), no additional invasive testing for systemic mastocytosis was performed.

Given the severity of the reaction and the risk of recurrence (54), it was decided that skin tests should be avoided and that a BAT should be performed as the primary diagnostic approach. This was performed 2 months after the initial reaction in accordance with the established protocol outlined in (6).

The BAT was found to be positive, showing a 22% net upregulation of the lysosomal associated membrane protein CD63 with ICG 6.45 μM and a 71% net upregulation with ICG 322.5 μM , thereby confirming an immediate immune-mediated reaction to the drug (Figure 1A). CD203c net upregulation was respectively 74% and 90% for the two concentrations tested. The test was also performed on three control subjects who had never been exposed to ICG, in whom no net upregulation of CD63 or CD203c was documented, thus reinforcing the specificity of the results observed in the patient (Figure 1B). As autofluorescence can impair the interpretability of the BAT results through spectral interference with fluorochrome probes, this was excluded for ICG. In fact, minor fluorescence was observed in the absence of fluorescent labeled antibodies.

To the best of our knowledge, this case represents the first in which an immediate immune-mediated drug reaction to ICG has been confirmed by the BAT. A review of the literature reveals that some cases have been documented via skin tests (7,8). However, a critical analysis reveals the absence of control tests on healthy individuals to exclude an irritant effect of the molecule, thereby limiting the interpretability of such results.

This case highlights the potential of the BAT as a primary diagnostic aid, enabling a diagnosis without exposing patients to skin tests that could potentially trigger a new severe systemic reaction. This is a particularly salient aspect in patients with a history of life-threatening anaphylaxis.

Furthermore, this case adds to the existing evidence supporting the use of the BAT as a reliable diagnostic tool for immediate immune-mediated reactions to dyes (8,9), provided that potential autofluorescence is appropriately excluded.

Also, using the BAT instead of skin tests circumvents the aesthetic concern of undesirable skin tattoos that can result from intradermal testing with dyes due to the retention in the dermis.

The BAT may also serve as a valuable tool not only for studying immediate immune-mediated reactions to ICG, but also for assessing potential cross-reactivity with structurally related compounds, such as infracyanine green. However, this investigation was not conducted in this instance due to the unavailability of infracyanine green in the Belgian drug formulary and the patient's refusal to undergo further testing.

The iodine content of ICG has often been cited in the literature as the alleged allergenic determinant responsible for immune-mediated reactions to the drug (11). However, this hypothesis remains unproven. The theoretical concern raised by some authors is not supported by the available clinical evidence. Indeed, large gynecological case series have not reported reactions to ICG among patients with a history of immune-mediated reactions to iodinated contrast media (12,13). Furthermore, no cross-reactivity between ICG and other dyes has been demonstrated to date.

Finally, future studies combining the BAT with the use of Bruton Tyrosine Kinase inhibitors, such as ibrutinib, may help elucidate the pathophysiological mechanisms underlying the immune-mediated drug reaction to ICG. This would provide further support for the hypothesis of an IgE-mediated mechanism (14). To date, no direct evidence supporting any specific pathogenic mechanism is available.

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Contribution

Conceptualization: AT, DE, VS; Visualization: CM; Writing – original draft: AT; Writing – review & editing: all the authors.

Conflict of interests

The authors have no conflict of interest to declare.

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Figure 1. A: CD63 and CD203c upregulation in patient basophils after exposure to ICG. B: CD63 and CD203c upregulation in patient compared to 3 unexposed controls.

