

# A Case of Severe Anaphylactic Reaction Secondary to Isosulfan Blue Dye Injection

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**Background:** Allergic reactions including anaphylaxis resulting from isosulfan blue dye are rare but warrant a thorough review given that lymph node mapping has become an increasingly common procedure, putting more patients at risk.

**Case Report:** Our patient was an 82-year-old female who underwent elective excision of a right forearm melanoma and right axillary sentinel lymph node mapping and suffered an anaphylactic reaction approximately 15 minutes after injection of isosulfan blue dye. The procedure was aborted. She was intubated; diphenhydramine and dexamethasone were administered; her blood pressure was stabilized with phenylephrine, epinephrine, and intravenous fluids; and she was transferred to the intensive care unit. She was extubated on postoperative day 1 and discharged home on postoperative day 2.

**Conclusion:** Sentinel lymph node biopsy is the standard of care for staging several cancers, and isosulfan blue is the dye most commonly used for this procedure. Reactions to the dye occur in some patients; however, we recommend the continued use of isosulfan blue dye for lymph node mapping given the low incidence of adverse effects, with no reported mortalities. Physicians should be prepared for the potential risk of anaphylactic shock.

**Keywords:** Anaphylaxis, isosulfan blue, sentinel lymph node biopsy

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## INTRODUCTION

Allergic reactions, including anaphylaxis resulting from isosulfan blue dye (also known as Lymphazurin), are well described in the literature, but lymph node mapping with isosulfan blue has become a common procedure and is the standard of care for accurate staging of breast cancer and melanoma. Allergic reactions to isosulfan blue occur unexpectedly and with unpredictable severity. Although these reactions are rare, surgeons performing these mapping procedures should be aware of the potential adverse events and be prepared to manage them.

## CASE REPORT

An 82-year-old female with a primary melanoma of her right forearm was admitted for elective excision of the melanoma with concomitant sentinel lymph node (SLN) mapping of her right axilla. Her melanoma was an amelanotic, superficial, spreading subtype, with a Breslow depth of 1.39 mm and a mitotic index of 4/mm<sup>2</sup>. No lymphovascular invasion or ulceration was found. Her medical history was significant for hypertension and arthritis. She had no history of myocardial infarction or stroke. She was evaluated for surgery with a preoperative electrocardiogram (EKG) that showed no change from her previous EKG, as well as a review of her most recent echocardiogram that was normal. Her basic laboratory results were unremarkable. She reported no known drug allergies.

On the day of the procedure, she underwent general anesthesia via laryngeal mask airway. Prior to sterile prepping and draping, 1 mL of isosulfan blue dye was injected intradermally, circumferentially around the site of the primary melanoma. We proceeded with the SLN mapping first. Our practice is to always use a dual-mapping technique, using blue dye as well as radioisotope mapping with technetium-99 sulfur colloid injected prior to the surgical procedure. We successfully removed the SLN and packed the axilla with a sterile laparotomy sponge. We then turned our attention to the site of the primary melanoma.

After we marked her skin with 2 cm margins, the patient became abruptly hypotensive and bradycardic. Rapid oxygen desaturation followed. The patient did not develop hives but shortly after developed a diffuse erythematous rash on most of her skin. This reaction occurred approximately 15 minutes after the injection of the isosulfan blue dye. Intravenous fluids were administered as a bolus, and vasopressor support was initiated with phenylephrine and epinephrine. Diphenhydramine and dexamethasone were also administered.

The procedure was aborted to stabilize the patient, and she was transferred to the intensive care unit because of continued hemodynamic instability requiring vasopressor support. She remained intubated, and a central venous line and an arterial line were placed. Cardiac enzymes, complete blood cell count, and chemistry panel values

were within normal limits. The patient significantly improved during the next 24 hours and was weaned off all vasopressor support. She was extubated the next morning and discharged home on the second day, with no significant residual complications noted. The patient returned to the clinic several weeks later, and we successfully removed her primary melanoma under a complete local anesthetic.

## DISCUSSION

The SLN mapping procedure has become the standard of care for the most accurate staging of breast cancer and melanoma. Isosulfan blue dye is often used for these procedures, and acute anaphylactic reaction to isosulfan blue dye is possible but uncommon. Leong et al reported a 0.74% incidence (3/406 cases) of anaphylaxis because of isosulfan blue dye for SLN mapping in melanoma in a series of 406 consecutive patients.<sup>1</sup> A similar incidence was reported in a review from Cimmino et al: 2/267 (0.75%) patients developed an anaphylactic reaction to isosulfan blue dye.<sup>2</sup> Among 2,392 SLN mapping procedures for breast cancer performed at Memorial Sloan Kettering Cancer Center between 1996 and 2000, a 0.5% incidence of anaphylactic reaction was noted as well as a 1.6% incidence of overall allergic reactions, such as urticaria, blue hives, or skin rash.<sup>3</sup> Of note, 2.6% (5/195) of patients who reported a sulfa allergy had an allergic reaction to isosulfan blue, but this incidence was not significantly different from those without a reported sulfa allergy.<sup>3</sup>

Case reports of allergic reactions including systemic anaphylaxis have been published since the introduction of SLN mapping in the 1980s.<sup>3-8</sup> These reactions vary in severity, with some biphasic reactions requiring a modified radical mastectomy to remove the excess dye in the breast tissue.<sup>1,7</sup> Most cases of anaphylaxis appear to be relatively short lived and nonlethal as long as the reaction is recognized and appropriately treated. Several strategies have been proposed to reduce the risk of life-threatening anaphylaxis because of isosulfan blue.

### Preoperative Testing

One possible solution for preventing an allergic reaction is to preoperatively evaluate and test each patient to confirm sensitivity to isosulfan blue dye. However, this approach is somewhat impractical, costly, and unreliable. Specifically, preoperative skin pricking has been proposed, but false negatives are more likely with skin prick compared to the more sensitive intradermal injection.<sup>9</sup> Other confirmatory tests for sensitivity to isosulfan blue include levels of plasma histamine, plasma tryptase, or urine methylhistamine at time of reaction or evaluation of radioimmunoassay or enzyme-linked immunoassay for drug-specific IgE serum antibodies.<sup>1</sup> These tests are often not feasible because the temporal relationship between reaction and laboratory testing is crucial. In reactions that range from hives to anaphylactic shock, the diagnosis is made clinically, and treatment is supportive.

### Prophylaxis

Empiric prophylaxis has also been studied in an attempt to reduce allergic reactions to isosulfan blue. In an effort to reduce the incidence and severity of adverse reactions to

isosulfan blue dye, Raut et al instituted a protocol of preoperative prophylaxis.<sup>10</sup> Adverse reactions were categorized into grade 1 (urticaria or blue hives, pruritus, or a generalized rash), grade 2 (hypotension not requiring vasopressors), or grade 3 (hypotension requiring vasopressor support). To patients receiving isosulfan blue dye, the team administered 100 mg of hydrocortisone (or 4 mg of dexamethasone), 50 mg of diphenhydramine, and 20 mg of famotidine intravenously just before or during induction of general anesthesia. Prior to implementation of the preoperative prophylaxis protocol, 7/639 patients had grade 3 reactions to dye (1.1%). With prophylaxis, 3/448 had grade 1 reactions (0.7%), and no grade 2 or grade 3 reactions occurred. Of patients receiving prophylaxis, no episodes of hypotension were observed, and no patients required vasopressors, ventilatory support, or intensive care observation. However, although prophylaxis decreased the severity of allergic reactions, the incidence of overall reactions was not significantly different. Additionally, Raut et al reported an increase in rates of infectious complications and wound dehiscence when preoperative prophylaxis was used.<sup>10</sup>

Further studies are required to analyze the risk-to-benefit ratio of a prophylactic regimen, given the low incidence of severe reactions and the potential adverse effects of steroids in particular.

### Decreased Dye Volume

The amount of dye used for SLN biopsy (SLNB) is not standardized, and the possibility exists that less dye volume may decrease allergic reactions. A prospective analysis found that the success rate of detection of the SLN did not differ depending on the amount of dye used, even in the dye-only technique.<sup>11</sup> Small amounts of dye ranging from 0.5-5.0 mL were used, and although not statistically significant, a trend toward a higher rate of allergic reaction with increased dye volumes was observed.<sup>11</sup> Our institution standardly uses 1 mL per draining nodal basin for melanoma and 2-3 mL total for breast cancer.

### Different Dye

Another possible solution to avoid allergic reactions to isosulfan blue dye is to simply use a different dye. No randomized controlled trials have compared methylene blue to isosulfan blue for SLN identification. Retrospective studies show identification rates using methylene blue are similar to rates when using isosulfan blue.<sup>12</sup> Case reports of SLNB using methylene blue include no reports of anaphylaxis, suggesting that methylene blue may be a safer dye for this procedure, although it is associated with more adverse skin reactions such as erythema and superficial necrosis than isosulfan blue.<sup>13,14</sup> Neves et al evaluated the rate of complications with the use of methylene blue dye vs isosulfan blue in SLNB in patients with skin cancer and found that methylene blue was associated with a significantly higher rate of superficial complications (8.7% vs 25.5%) and skin graft rejections (0% vs 50%).<sup>15</sup> Clearly, the use of methylene blue is not without risk. Two cases of severe hypotensive shock have been reported in response to intrauterine injection of methylene blue dye.<sup>16,17</sup>

In addition, cross-reactivity between patent blue dye, an isomer of isosulfan blue dye, and methylene blue has been

reported in melanoma patients who underwent SLNBs, suggesting that patients with a sensitivity to isosulfan blue may also have a sensitivity to methylene blue.<sup>18</sup> Finally, methylene blue may not be the most effective dye for SLNB based on its chemical structure. Specifically, it has a lower molecular weight than isosulfan blue, and because of its lack of sulfonic acid groups, it does not bind to lymph proteins and instead continues to the blood capillaries. These properties may lead to a less accurate removal of SLNs.<sup>19</sup> Further research through randomized controlled trial or metaanalysis is needed to compare the safety and efficacy of methylene blue to isosulfan blue. Isosulfan blue continues to be the most frequently used blue dye in the United States.

### No Dye

Perhaps the most logical solution to prevent adverse reactions to isosulfan blue is to remove blue dye from lymph node mapping altogether. We routinely perform dual-method SLN mapping with injection of both isosulfan blue dye and radioactive technetium-99 sulfur colloid. Gershenwald et al examined this technique and reported that SLNB for melanoma performed using both isosulfan blue dye and radiocolloid injection is highly accurate, with an identification rate of 93%-97% (depending on the node basin).<sup>20</sup> A more recent review of SLNB for melanoma replicated these findings with dual-agent mapping and recommended SLNB for lesions 1 mm or thicker, <1 mm with ulceration, Clark level IV, or high mitotic rate, as SLNB has consistently been shown to accurately stage melanomas that are stage I and II with minimal morbidity.<sup>21</sup>

Other studies, however, indicate that radiocolloid as a single mapping agent is just as effective in SLN identification as the dual-mapping technique.<sup>22,23</sup> Surgeon experience with the procedure is important, as it significantly affects SLN identification and accuracy rates.<sup>24,25</sup> One study recommends the combined approach but only for inexperienced surgeons.<sup>25</sup> Although reports conflict, several publications continue to support the dual method for improved accuracy.<sup>26</sup> A review of the literature on the use of blue dye only for SLNB in early breast cancer notes the lack of reliably reproduced data showing that single-agent mapping with radiocolloid only is comparable or superior to the dual method of SLNB. The review recommends the continued use of blue dye in combination with radiocolloid, as the severe risks are extremely uncommon and manageable with no reported mortality as a result.<sup>27</sup>

### CONCLUSION

SLNB is now regarded as the standard of care for the staging of several cancers, particularly breast cancer and melanoma. Lymphatic mapping usually involves SLN identification with isosulfan blue dye as well as radioactive sulfur colloid injection. Although isosulfan blue dye can cause allergic reactions, most reactions are not severe, unlike the anaphylactic shock seen in this case. Little compelling data show an advantage of a single agent for mapping, either blue dye only or radiocolloid only, and thus we recommend dual-agent mapping with isosulfan blue and radiocolloid. Unfortunately, no current validated method detects or decreases the risk of allergic reaction, and more research is needed in this area. Although rare, physicians

should be prepared for the potential risk of anaphylactic shock for all patients who are scheduled to undergo an SLNB. Appropriate and immediate recognition of a blue dye reaction is critical to proper management.

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