A Cautionary Tale: Anaphylaxis to Isosulfan Blue Dye after 12 Years and 3339 Cases of Lymphatic Mapping

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Sentinel node biopsy has become the standard method for lymphatic staging in early-stage breast cancer and melanomas. The most commonly used technique uses both a radioactive tracer as well as blue dye, usually isosulfan blue. In this report, we discuss two episodes of anaphylaxis to isosulfan blue during lymphatic mapping, occurring 12 years and 3339 lymphatic mapping cases after adoption of the technique, and discuss management issues raised by these events.

THE CONCEPT OF SELECTIVE staging of the draining nodal site for malignancy has evolved over the last 30 years.[1] The introduction of lymph node mapping by Cabanas in his treatment of patients with penile cancer in 1977 opened the possibility for its adaptation to other malignancies.[2] This concept was applied to melanoma and described by Morton in 1992.[3] Giuliano then quickly followed with his description of lymph node mapping for breast cancer.[4] Today, sentinel node biopsy is routinely used for staging the nodal basins in clinically node-negative breast cancer and melanoma. In our institution, technetium-99m-labeled sulfur colloid and 1 per cent isosulfan blue dye have been used in combination for lymphatic mapping over the last 13 years. We recently experienced our first two cases of anaphylaxis during lymphatic mapping and discuss how this experience has changed our operative approach based on the relevant available literature.

Case Reports

Case 1

A 62-year-old woman presented with a palpable, well-defined, 3-cm lesion in the upper-outer quadrant of her right breast. This lesion was radiologically occult on mammogram and breast ultrasound. The patient had a surgical history significant for laparoscopic cholecystectomy and gastric bypass. She had no known drug allergies. She declined preoperative fine needle aspiration biopsy for cytopathology; subsequent excisional biopsy demonstrated high-grade comedo-type ductal carcinoma in situ with close surgical margins and probable microinvasion.

A second surgery was scheduled for re-excision of the surgical margins as well as sentinel node biopsy. Preoperatively, the patient underwent subareolar injection with technetium-labeled sulfur colloid in the nuclear medicine department. Once in the operating room, general anesthesia was induced, a laryngeal mask airway inserted, and 1 g cefazolin administered intravenously. Five millimeters of isosulfan blue was injected adjacent to the previous surgical excision and massaged into the subcutaneous tissue. The sentinel lymph node biopsy was completed with the successful identification of two blue radioactive nodes. Frozen section analysis revealed no evidence of metastatic spread, and the re-excision was started.

Within 30 minutes of injecting the isosulfan blue, the patient suddenly became hypotensive and tachycardic with a blood pressure of 60/20 mm Hg and a pulse rate of 160 beats/min. The patient's oxygen saturation decreased from 100 per cent to 84 per cent. Ephedrine and Neo-Synephrine boluses were administered, the inhalation anesthetic was decreased, the laryngeal mask airway removed, and the patient endotracheally intubated. An arterial line and a central venous catheter were placed. Her central venous pressure was 5 to 10 mm Hg. She remained hypotensive and tachycardic. Next, Solu-Medrol, epinephrine, and Benadryl were injected intravenously with immediate improvement in the patient's hemodynamics. An intraoperative echocardiogram demonstrated normal wall motion and ejection fraction.

Approximately 10 minutes later, her blood pressure again dropped, requiring additional steroid and Benadryl administration. The surgical incision was closed and the patient transported to the recovery room on a continuous epinephrine drip. Once in the recovery room, the patient awoke and remained hemodynamically stable on a low dose of epinephrine. She remained intubated overnight because of laryngeal edema. She was extubated the next morning and discharged home on the second postoperative day on a ste-

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roid taper, oral antibiotics, and vitamin A. She was subsequently evaluated by an allergist, and no drug allergies were demonstrated with the conclusion that this episode was indeed an anaphylactic response to isosulfan blue.

Case 2

The second case involved a 77-year-old man who presented with a melanoma of his right back. His medical history was significant for hypertension, chronic renal insufficiency, gout, and hypercholesterolemia. He had undergone surgical repair of a femur fracture. The patient was taking the following prescription medications: atenolol, allopurinol, hydrochlorothiazide, aspirin, pravastatin, Zetia, and enalapril. He did not have any known drug allergies. A biopsy of the lesion demonstrated a 2-mm thick malignant melanoma without evidence of ulceration but with regression. A preoperative positron emission tomography–CT scan was negative for metastatic disease.

The patient was injected with technetium sulfur colloid in the nuclear medicine suite the morning of surgery. Once in the operating suite, the patient was intubated and 1 g of cefazolin was given. The patient was then turned onto his side so that 1.8 cc of the isosulfan blue could be injected intradermally. The patient was then prepped and draped after massaging the area of injection for approximately 10 minutes. Two blue nodes were identified and removed from the right axilla.

The patent suddenly became hypotensive. Intravenous Decadron, methylprednisolone, and Benadryl were administered. An epinephrine drip was started. Invasive monitoring was secured and the axillary incision was closed. After obtaining hemodynamic stability, a wide and deep excision of the lesion, including the visible injected blue dye, was completed. The patient was then transported to the recovery room on an epinephrine drip. Throughout the first postoperative day, the patient had continued green–blue-colored urine. The use of steroids continued throughout this period of his hospital course. On the second postoperative day, the patient no longer required vasopressor support and was successfully extubated. The patient was discharged home on the third postoperative day on an oral steroid taper.

Discussion

The use of the sentinel node technique to stage the nodal basins in patients with both invasive breast cancer and melanoma has been in practice at our institution since the early 1990s with a total of 3339 cases performed from January 1995 to March 2007. We have routinely used both technetium-labeled sulfur colloid and isosulfan blue for lymphatic mapping. During this time period, there were no episodes of anaphylaxis until the two described cases occurred. These two episodes have been the impetus for reevaluating our management of sentinel node biopsy.

These two cases are similar to other cases of anaphylaxis reported in the literature.[5–15] The delayed onset, between 30 and 40 minutes after dye injection, the requirement for steroids and epinephrine to obtain hemodynamic stability, and the ineffectiveness of pressor agents is consistent with the diagnosis and treatment of previously described events in the literature.

Both patients in our series experienced severe reactions necessitating ventilator support, invasive monitoring, and the administration of vasopressors, glucocorticoids, and antihistamines. In the patient with melanoma, the additional therapeutic maneuver of removing the tissue surrounding the primary lesion that had been injected with isosulfan blue was performed to remove any residual antigenic material.

The available reports discussing anaphylaxis after lymphatic mapping with isosulfan blue are summarized in Table 1. The recent report of the American College of Surgeons Z10010 trial is the largest series available to date with an incidence of anaphylaxis to isosulfan blue of 0.1 per cent reported in 4975 patients.[15] The unpredictability and rarity of anaphylaxis is illustrated by the variation in incidence in the reported series.

In view of this experience, there has been interest in switching from isosulfan blue to methylene blue as a result of its limited risk for severe allergic reactions.[14, 16–18] A recent review of the literature suggests that methylene blue is able to identify the sentinel lymph node with an accuracy of 97 per cent, comparable to published rates of sentinel node identification using isosulfan blue.[19] There have been no reported cases of anaphylaxis from the use of methylene blue in the identification of the sentinel lymph node in cases of melanoma or for breast cancer.[20–22] The only report of possible methylene blue anaphylaxis is in the obstetrics literature, discussing the case of a woman undergoing tubal permeability assessment using methylene blue, who developed severe anaphylaxis. She became hypotensive and, unlike the isosulfan blue cases, responded to epinephrine.[7] This is inconsistent with dye-induced anaphylaxis, especially in light of

TABLE 1. *Incidence of Anaphylaxis to Isosulfan Blue: Reported Series*

Series (year)	Incidence of Anaphylaxis (no. of episodes/no. of cases)
Leong[25] (2000)	0.7% (3/406)
Albo[5] (2001)	1.1% (7/639)
Cimmino[26] (2001)	0.8% (2/267)
Montgomery[10] (2002)	0.5% (9/2464)
Wrightson[27] (2003)	0% (0/2120)
Komenaka[9] (2005)	0% (0/351)
Raut[13] (2005)	0% (0/679)
Wilke[15] (2006)	0.1% (5/4975)
Current study (2007)	0.06% (2/3339)
Combined series	0.2% (28/15,260)

recent investigations using methylene blue as a treatment for refractory septic shock.[23] It is certainly possible that anaphylaxis has not yet been described with methylene blue as a result of the overall rarity of these events and more common use of isosulfan blue for lymphatic mapping.

Skin necrosis and abscess formation with intradermal injection of methylene blue have been reported as a potential serious adverse event, although the overall incidence is unknown.[24] In view of this potential side effect, there has been recent interest in use of dilute methylene blue for mapping.[16]

Although isosulfan blue contains sulfur, there is no evidence that a known sulfur allergy predisposes to anaphylaxis in an individual exposed to isosulfan blue, and our first patient tested negative for a sulfur allergy. The common use of the triphenylmethane-related dyes in consumer products such as cosmetics, leather, and textiles is considered the likely source of previous exposure and sensitization to these dyes.[14] The ubiquitous commercial use of these dyes has been used as a rationale for routine prophylaxis against anaphylaxis after use of isosulfan blue. A recent study concluded that the use of a prophylactic regimen, including glucocorticoids, histamine blockers, and an antihistamine, reduced the severity of reactions but not the incidence of overall events.[13] As a result of the rarity of these events, the statistical power of this study may not have been large enough to capture possible anaphylactic events. In addition, this study reported a twofold increase in the rates of infectious complications and wound dehiscence. Although these reported results were not statistically significant, they should not be discounted when considering using preoperative prophylaxis.

In summary, anaphylaxis to isosulfan blue is rare and unpredictable with an incidence of approximately 0.2 per cent. Anesthesiologists and surgeons need to be prepared for these unpredictable occurrences, which, as demonstrated by our experience, may not occur until after many years and thousands of cases of mapping with isosulfan blue. The increased recognition of these reactions has led to changes in clinical practice, including the substitution of methylene blue for isosulfan blue and interest in using dilute dye.

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