

Patent Blue Dye and An Atypical Anaphylactic Reaction After Sentinel Lymph Node Biopsy in Early Breast Cancer

To the Editor:

Lymphatic mapping and sentinel node biopsy are routinely used in staging early breast cancer. Technetium-99 m labeled sulfur colloid and blue dye (commonly Patent Blue or its isomer, Isosulfan Blue) are used either alone or in conjunction to delineate the lymphatic drainage of a tumor to its sentinel lymph node. Allergic reaction and anaphylaxis have been observed in 1–3% of patients exposed to the dye (1). Although being rare, the spectrum of response can range from a mild allergic reaction with urticaria to anaphylaxis associated with cardiovascular and respiratory collapse. With the increasing use of sentinel node techniques for other indications, e.g., melanoma, bladder cancer, and endometrial cancer, the incidence of allergic reaction to blue dye can be expected to rise.

A 38-year-old woman with early breast cancer was scheduled for a wide local excision and SLN biopsy. Her past medical history consisted of borderline hypertension and mild peripheral edema for which she was on a trial of furosemide.

On the morning of surgery, the patient was given technetium-labeled colloid by Nuclear Radiology and after the induction of general anesthesia, 2 cc of Patent Blue dye was injected peri-tumourly. Two hours later, while the surgeons were closing, the anesthetist noted new onset tachycardia and hypotension with systolic blood pressures in the range of 50–60 mmHg. Aggressive fluid resuscitation and vasopressors were started. The drapes were removed, and there was no evidence of urticaria. Oxygen saturations remained over 90% throughout the resuscitation and good air entry bilaterally was auscultated without bronchospasm.

With ongoing resuscitation and the addition of anti-histamines and high dose steroids, her systolic pressure stabilized at over 100 mmHg. She was extubated and transferred to the surgical step-down unit for continued hemodynamic monitoring. Postoperatively, reassessment of her extremities revealed a coalescing erythematous rash. The patient was diagnosed with probable anaphylactic reaction to Patent Blue dye. The following day she had stabilized and was discharged home. Follow-up skin prick testing with an allergist revealed a positive wheal and flare reaction to the blue dye.

This case provides an example of a severe and life-threatening anaphylactic reaction to Patent Blue dye manifested only by cardiovascular collapse and skin rash, without concomitant respiratory compromise or bronchospasm.

Patent Blue dye and its isomer isosulfan blue belong to the group of triarylmethane dyes, and exhibit cross-reactivity due to their chemical similarity. Due to its widespread use within the textile, paper, and agricultural industries, in addition to its medical application, exposure and sensitization have probably occurred in a large percentage of the population (2). Three distinct patterns of allergic response have been noted: grade 1 (urticaria, pruritus, generalized rash), grade 2 (transient hypotension not requiring vasopressors), and grade 3 (severe hypotension requiring vasopressor support) (1).

Anaphylactic reactions to blue dyes have previously been reported in a number of case reports, as well as several retrospective and prospective studies. Montgomery *et al.*, (1) performed a meta-analysis of multiple single-institution series as well as a retrospective review of their own 2,392 patients receiving blue dye for sentinel mapping in breast cancer at MSKCC. They calculated the incidence of allergic reaction to be 0.6–2.7%, with a mean of 1.8%, in those receiving Patent Blue. The majority (69%) of these reactions were grade 1 reactions. Anaphylaxis with hypotension was noted in 0.5%.

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A preoperative prophylactic regimen of 100 mg of hydrocortisone, 50 mg of diphenhydramine, and 20 mg of famotidine has previously been reported (3). Raut *et al.*, found the incidence of allergic reaction in this pretreated group to be 0.5%, which was not significantly different from their reported general incidence of 1.1%. However, all affected patients had grade I reactions. No episodes of hypotension were noted, and no patient required vasopressors, ventilatory support, or observation within an intensive care. They concluded that the severity, but not the overall incidence, of allergic reaction to isosulfan blue could be reduced with preoperative prophylaxis.

Given the risk of allergy with blue dye, some have questioned its continued use in mapping sentinel lymph nodes. Some suggest that in experienced hands, there does not appear to be a significant difference in detection of sentinel lymph nodes when radioisotope is used alone or in conjunction with isosulfan blue dye, with an SLN identification rate greater than 95% (4). The ability to identify the sentinel node with blue dye does not seem to improve with operator experience, while successful localization using radioisotope does (5). For surgeons with less experience, the combination of both agents improves successful identification, and still affords the highest technical success and lowest false-negative rates (6).

Methylene blue has been proposed as a safer alternative to Patent Blue or isosulfan blue dye for lymphatic mapping in breast cancer (7). Varghese *et al.*, reviewed 329 patients with early breast cancer undergoing methylene blue dye sentinel node localization, with and without radioisotope tracer. They reported no incidents of allergic reaction or tissue necrosis, with transient skin tattooing being the only adverse effect. The efficacy of methylene blue in identifying the sentinel node has also been studied, with a reported 92% success rate in identifying the sentinel node with methylene blue alone, improving to 95.5% when combined with technetium-labeled sulfur colloid (8). These rates compare favorably with those of Patent Blue and isosulfan blue dye. Methylene blue appears to be a safe and effective alternative to other dyes for sentinel node mapping; however, with only a fraction of surgeons using methylene blue in breast cancer lymphatic mapping, the true incidence of allergic reaction remains to be seen.

In conclusion, sentinel node mapping is a common procedure in the staging and management of early

breast cancer. Commonly used agents include Patent Blue dye and its isomer isosulfan blue, and allergic reactions can be expected in up to 3% of patients, with the majority of reactions being mild. Our case highlights the rare but potentially life-threatening incidences of anaphylaxis associated with administration of Patent Blue dye. Anaphylaxis does not always present with all the hallmarks of a classic reaction, and prompt recognition by the treating team is required. Preoperative prophylactic regimens with intravenous glucocorticoids and antihistamines reduce the severity, but not overall incidence, of allergic reactions. Recent reports suggest that methylene blue is a safer and equally efficacious substitute in sentinel node mapping; however, a large prospective investigation comparing this agent with the more common triarylmethane dyes has yet to be undertaken.

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