Anaphylaxis during sentinel lymph node mapping

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CASE

Mammography was performed in a healthy 54-year-old female and uncovered a 7-mm solid lesion in the right breast. A biopsy of the lesion revealed invasive carcinoma surrounded by ductal carcinoma in situ. The patient had no family history of breast cancer and no history of smoking, excessive alcohol consumption, asthma, or allergies. Her medical and surgical histories included hysterectomy and tonsillectomy. She reported that she was allergic to cephalexin. Daily medications included aspirin (81 mg), a multivitamin, and estrogen replacement, which was discontinued at the time the breast cancer was diagnosed. The patient was scheduled for a lumpectomy with axillary node sampling using isosulfan blue and technetium (99m Tc) sulfur colloid.

A total dose of 0.5 mCi of 99m Tc was administered approximately 2 hours and 45 minutes before the patient's arrival in the OR. She also received a preoperative dose of clindamycin, 900 mg IV, to which she experienced no adverse reaction. General anesthesia was then induced with desflurane administered via a laryngeal airway mask; dexamethasone, 8 mg, and ketorolac, 60 mg, were also administered IV. Vital signs were stable with a BP of 144/71 mm Hg, a heart rate of 100 beats per minute (bpm), and pulse oxygen saturation of 97%. The patient was prepped and draped in normal sterile fashion. Isosulfan blue, 5 mL, was injected in the circumareolar breast region. A right breast lumpectomy was then performed and included the removal of moderate amounts of tissue surrounding the tumor site.

Approximately 20 minutes after the administration of the isosulfan blue, the patient abruptly became severely bradycardic, hypoxemic, and hypotensive with a BP of 44/19 mm Hg, a heart rate of 45 bpm, and an oxygen saturation of 88%. The anesthesiologist quickly performed endotracheal intubation. The patient was aggressively resuscitated with lactated Ringer's solution administered at 1,000 mL/h, and a continuous dopamine infusion was started. Diphenhydramine, 50 mg, was also administered by IV push. Because of the patient's unstable hemodynamic status, the sentinel node mapping technique was aborted and a rapid axillary node sampling procedure was performed. The axillary incision was quickly closed, while a femoral arterial line was then started for continuous monitoring of arterial pressure. The patient was then transferred to the ICU for further diagnostic evaluation and resuscitation.

Once in the ICU, the patient continued to receive fluids and dopamine, and her BP increased to 105/60 mm Hg and her heart rate to 88 bpm. She was started on mechanical ventilation. Physical examination revealed significantly swollen upper extremities, including the head, neck, lips, and ear lobes. It was then assumed that the patient also was suffering from pronounced upper airway swelling.

Subsequent treatment included diphenhydramine, 50 mg IV every 6 hours; methylprednisolone, 125 mg IV every 6

hours; famotidine, 20 mg IV twice daily; and a continuous infusion of propofol for sedation. Once cardiovascular stability was achieved, the dopamine infusion was tapered down and eventually discontinued.

Despite propofol administration, the patient became agitated and extubated herself after two days of being intubated. Multiple attempts were made to reintubate the patient without success. Bronchoscopy was then used to complete a successful reintubation.

Bronchoscopic visualization showed significant edema of the oral cavity, larynx, trachea, carina, and right and left mainstem bronchi, causing an almost complete loss of the architectural appearance of the larynx. After reintubation, an oxygen saturation of 100% was achieved. The patient was placed on a continuous infusion of rocuronium in addition to the propofol to prevent any further episodes of self-extubation. She continued to receive corticosteroids and diphenhydramine, and she remained on mechanical ventilation for 9 days. She was then extubated without complications. Muscle weakness was noted and was considered to be most likely a result of the combination of rocuronium and corticosteroids. Physical therapy was started, and the patient improved. After a total of 13 days in the hospital recovering from a presumed anaphylactic reaction after the administration of isosulfan blue, the patient was discharged.

DISCUSSION

Isosulfan blue can be used alone or in conjunction with a radionucleotide for sentinel lymph node mapping in breast cancer patients. The dye is administered subcutaneously at the site of the tumor or in the area around the nipple. It accumulates into the lymphatic system and the lymph nodes collect the dye, which causes them to appear blue when dissected operatively. If the sentinel lymph nodes are microscopically free of metastases, the rest of the axillary nodes need not be removed. If the sentinel node is positive for metastatic spread, further nodal dissection is done to accurately stage the disease.[1]

Isosulfan blue is a 2,5 disulfonated isomer of patent blue dye and is the only vital dye approved by the FDA for use in sentinel lymph node mapping.[2] Isosulfan blue has no known pharmacologic action. As with any drug, however, its use can produce side effects or allergic reactions.

The first known allergic reaction to isosulfan blue dye was documented in 1985.[3] However, product information for isosulfan blue 1% states that incidence of adverse effects using this type of dye is 1.5%, all of which were allergic reactions ranging from mild to severe.[2] Mild reaction can occur within several minutes of administration and include localized swelling at the injection site and mild pruritus of the hands, abdomen, and neck.[2] Severe reactions include edema of the

face and glottis, respiratory distress, and shock.[2] Severe reactions may be fatal unless appropriate emergency measures are immediately taken. An adverse reaction to isosulfan blue is more likely to occur in patients with a personal or family history of bronchial asthma, significant allergies, or a history of a drug reaction to triphenylmethane dyes.[2]

A review of literature provides multiple examples of adverse reactions to the dye. In a study at the Memorial Sloan-Kettering Cancer Center, adverse reactions to isosulfan blue dye occurred in 39 of 2,392 patients; only 9 patients became hypotensive and required vasopressor support.[4] The remaining adverse reactions included urticaria, blue hives, a generalized rash, and pruritus. A study performed by King and colleagues looked at the adverse effects associated with isosulfan blue in sentinel lymph node mapping.[5] Their study yielded 31 adverse reactions in 1,728 patients.[5] Urticaria, blue hives, a generalized rash, and pruritus were noted in 27 patients; one patient experienced transient hypotension but did not require vasopressor support, and two other patients also experienced transient hypotension and were successfully treated with diphenhydramine, corticosteroids, and vasopressors.[5] One of the two patients requiring vasopressor support also required a single bolus of epinephrine, after which the hypotension resolved.[5] One patient was noted to have a decreased oxygen saturation level with no other notable signs or symptoms of an allergic reaction.[5] No patients required intubation or sedation as a result of an allergic reaction to isosulfan blue.[5] A similar study by Albo and colleagues documented 7 adverse reactions in 639 patients; all 7 patients required vasopressor support.[6] A fourth study completed at Columbia-Presbyterian Breast Center in New York City yielded 3 allergic reactions out of 351 subjects undergoing sentinel lymph node mapping with isosulfan blue.[7] All three patients had mild reactions limited to blue hives.

TABLE 1. Managing anaphylaxis

Urticaria, pruritus, or minimal localized swelling only
• Treat with antihistamine (diphenhydramine, ranitidine) • Monitor vital signs
Respiratory and hemodynamic instability with hypotension (with or without urticara or pruritus)
• Administer epinephrine IM • Treat with antihistamine (diphenhydramine, ranitidine) • Provide aggressive fluid resuscitation • Administer vasopressors (dopamine/norepinephrine) for persistent hypotension • Monitor vital signs • Consider arterial line and admission to ICU
Respiratory and hemodynamic instability with hypoxia (with or without urticara or pruritus)
• Administer epinephrine IM • Treat with antihistamine (diphenhydramine, ranitidine) • Administer oxygen • Intubate and provide mechanical ventilation for continued respiratory distress • Continue to monitor oxygenation

Data from McPhee SJ, Papadakis MA, Tierney LM Jr. *Current Medical Diagnosis and Treatment.* 44th ed. New York, NY: Lange Medical Books/McGraw-Hill; 2005.

CONCLUSION

Sentinel lymph node mapping has become a common procedure for patients with breast cancer or melanoma and is now being considered for those with colon cancer.[1] The procedure allows for accurate removal of sentinel nodes with a low association of comorbidities. Isosulfan blue is an inert, nonpharmacologically-acting dye commonly used in the mapping of sentinel lymph nodes. It can be used alone or, most commonly, with a radionucleotide such as 99m Tc sulfur colloid. Isosulfan blue has become the popular agent for sentinel node mapping technique because of a low incidence of adverse reactions, which occur in 1.5% of patients.[2] The patient in this case had a serious anaphylactic reaction—one of the most severe and least common involving isosulfan blue. Although the risk of an adverse reaction is low, patients should be made aware of the potential risks involved, and clinicians administering isosulfan blue should be prepared to manage any adverse reactions (see Table 1). JAAPA

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DRUGS MENTIONED

Cephalexin (Keflex Pulvules)
Clindamycin (Cleocin)
Desflurane (Suprane)
Dexamethasone
Diphenhydramine
Dopamine
Epinephrine
Estrogen (Premarin)
Famotidine (Pepcid I.V.)
Isosulfan blue (Lymphazurin)
Ketorolac (Toradol)
Methylprednisolone (A-methaPred, Depo-Medrol, Solu-Medrol)
Propofol (Diprivan)
Ranitidine (Tritec, Zantac)
Rocuronium (Zemuron)
Technetium (99m Tc) sulfur colloid

REFERENCES

1. Darzi A, Mackay S. Recent advances in minimal access surgery. *Br Med J.* 2002;324(7328):31-34.
2. Lymphazurin 1% [package insert]. Bedford, OH: Ben Venue Laboratories Inc; 2003.
3. Longnecker SM, Guzzardo MM, Van Voris LP. Life-threatening anaphylaxis following subcutaneous administration of isosulfan blue 1%. *Clin Pharm.* 1985;4(2):219-221.
4. Montgomery LL, Thorne AC, Van Zee KJ, et al. Isosulfan blue dye reactions during sentinel lymph node mapping for breast cancer. *Anesth Analg.* 2002;95(2):385-388.
5. King TA, Fey JV, Van Zee KJ, et al. A prospective analysis of the effect of blue-dye volume on sentinel node mapping success and incidence of allergic reaction in patients with breast cancer. *Ann Surg Oncol.* 2004;11(5):535-541.
6. Albo D, Wayne JD, Hunt KK, et al. Anaphylactic reactions to isosulfan blue dye during sentinel lymph node biopsy for breast cancer. *Am J Surg.* 2001;182(4):393-398.
7. Komenaka IK, Bauer VP, Schnabel FR, et al. Allergic reactions to isosulfan blue in sentinel lymph node mapping. *Breast J.* 2005;11(1):70-72.