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CASE REPORT

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Severe anaphylactic reaction after blue dye injection for sentinel lymph node biopsy in breast surgery: Report of two cases and literature review

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Abstract

Anaphylactic reactions, and especially the severe ones (types III and IV), should be kept in mind as considerable adverse effects while using blue dyes for SLNB.

KEYWORDS

acute medicine, allergy and immunology, critical care medicine, general surgery

1 | INTRODUCTION

Patent blue V is the most common dye used for sentinel lymph node mapping. We reported two cases of anaphylactic shock after patent blue V injection for sentinel lymph node biopsy (SLNB). 57 cases of severe anaphylactic reaction triggered by blue patent V have been reported so far.

Sentinel lymph node biopsy (SLNB) is the standard of care for accurate axillary staging in clinically node-negative breast cancer patients.[1] In addition, SLNB is included in the surgical treatment of invasive melanoma and its role in gastric, thyroid, and colonic cancer is under investigation.[2,3] The use of a blue dye for lymphatic mapping, either alone or in combination to a radio-isotope, seems to increase the SLN identification rate; thus, blue dyes—especially patent blue violet (V) in Europe—have been widely used for SLNB. Blue dyes have been associated with a minor risk of anaphylactic reaction that ranges from simple cutaneous manifestations to anaphylactic shock.[4] We present two cases of severe anaphylactic reaction after patent blue V dye injection for SLNB in two early-stage breast cancer patients.

2 | CASE ONE

A 69-year-old woman with a 2 cm palpable mass in the upper outer quadrant of her right breast, which was proved as an invasive ductal carcinoma after core biopsy, was scheduled for breast-conserving surgery with SLNB. Her past medical history included arterial hypertension, smoking, and G6PD deficiency. As per institutional guidelines, 2ml of patent blue V was injected subcutaneously into the periareolar area of the right breast after intubation of the patient in the operating theater and gentle massage of the injection site followed.

Approximately 10 minutes following dye injection, the patient developed tachycardia (118 beats/min) and hypotension (systolic blood pressure: 58 mm Hg). However, no electrocardiographic alterations were observed. In addition, an intense flushing on her face and torso was manifested. Her arterial blood gas examination showed a mild increase in serum lactate levels (2.4 mmoL/L), whereas her serum troponin value was normal (7.9 pg/mL). Intravenous fluid resuscitation (2 L of crystalloids and 0.5 L of colloids) was promptly commenced, along with intravenous administration of epinephrine and hydrocortisone. Approximately 15 minutes after the episode started, the hemodynamic stability of the patient had been fully restored and the skin erythema subsided. The surgical procedure (wide local excision and SLNB) was completed after 80 minutes, and the patient was transferred to the intensive care unit (ICU) for postoperative monitoring.

Her postoperative course was uneventful. After 24 hours at the ICU, she was transferred to the surgical ward, where she remained for 24 hours before being discharged home. The patient was examined at the allergy department, where allergy to patent blue V was revealed.

3 | CASE TWO

A 51-year-old woman was scheduled for breast-conserving surgery with SLNB due to a ductal carcinoma in her right breast that was identified during her mammographic screening examination. Her past medical history included autoimmune hypothyroidism, and she was a heavy smoker.

Similarly to the previous case, 2 mL of patent blue V was injected subcutaneously and an oncoplastic resection was performed as well as SLNB. Approximately 15 minutes after procedure initiation, the patient manifested signs of severe anaphylactic reaction with sudden hypotension (systolic blood pressure: 38 mm Hg) and tachycardia (140 beats/min), without electrocardiographic alterations though. A significant rash in her face and torso was also observed. Arterial blood gas was normal, apart from a mild lactic acidosis. Administration of large volumes of crystalloids (3L) and colloids (1L), along with an intravenous dose of hydrocortisone and epinephrine, led to hemodynamic stabilization of the patient. The procedure was completed under continuous administration of low-dose intravenous vasopressors. The patient recovered smoothly from anesthesia approximately 2 hours later and was transferred to the surgical ward for postoperative monitoring.

Her postoperative course was uneventful and she was discharged home 24 hours later. Allergy to patent blue V was again diagnosed at the allergy dept.

4 | DISCUSSION

About 20 years ago, Nos et al indicated that blue dye was suitable as the only method of SLN mapping in patients with small or medium-sized breasts and low body fat that underwent SLNB prior to tumor excision.[5] Nevertheless, Kim et. al demonstrated in their meta-analysis that the combination of colorimetric and isotopic mapping increases the SLN identification rate from 83.1% (blue dye alone) to 96.4%.[6] Apart from that, the combination of the two methods reduced the required time for surgical training, as the surgical dissection by following the colored lymphatic tract is much easier. The most commonly used blue dyes for SLNB are isosulfan blue in the United States and patent blue V in Europe that both belong to the group of triarylmethan dyes and actually share the same formula except from an additional hydroxyl group for patent blue V.[7] Blue dyes act as foreign bodies after injection in a patient's body. Therefore, several allergic reactions against blue dyes have been reported in the literature, the incidence of which varies between 0.06% and 2.7%, with a mean value of 0.71%. Fortunately, the reported risk of severe allergic reactions, that required vasopressors' administration or surgery interruption, remains extremely low and barely reaches 0.1%.[8]

Anaphylactic reactions to blue dyes seem to be mediated by IgE antibodies (type I) after the configuration of a structure completely dependent on patent blue V that acts as hapten and is linked to a, so far, unknown carrier which seems to be unique for patients that have experienced a blue dye-induced anaphylactic reaction. Consequently, there has been no association between a patient's history of atopy or previous allergy to any drugs, such as penicillin, and predisposition to anaphylactic reaction against patent blue V so far.[9] In addition, there is no test to predict a potential allergic reaction against patent blue V, as special antibodies that never existed before, appear after trigger exposure. Nevertheless, some centers avoid patent blue V administration in patients with a previous history of allergy in any drugs. On the other hand, preoperative prophylaxis, that consisted of glucocorticoid, diphenhydramine and famotidine, in patients with a previous history of allergy seemed to reduce the severity of anaphylactic reactions against blue dyes, but not their overall incidence.[10]

Intraoperative anaphylactic reactions are classified in four types according to their severity [11]: Type I includes reactions only with cutaneous manifestations such as urticaria, pruritus, blue hives, or generalized rash. Type II includes reactions with additional tachycardia and hypotension, but with a decrease of no more than 20 beats/min or 20 mm Hg, respectively. Type III includes reactions with a refractory shock (systolic pressure < 70 mm Hg) that usually require vasopressor support and intensive care unit (ICU) administration. Type IV reactions refer to cardiac arrest. Type I and II anaphylactic reactions may resolve with 100% oxygen delivery, fluid resuscitation (up to 4L of colloids or crystalloids), antihistamines (chlorpheniramine), corticosteroids, and bronchodilators (salbutamol). Type III anaphylactic reactions may require vasopressors (epinephrine) administration, whereas type IV reactions demand immediate cardiopulmonary resuscitation. In some cases, a biphasic anaphylactic reaction has been described, with hypotensive episodes occurring at 15 minutes and 2 hours after blue dye injection, in which corticosteroids seem to have a protective action.[12]

Our study is the first which reviews severe (types III and IV) anaphylactic reactions after patent blue V injection for SLNB in breast surgery. Only 57 patients that experienced severe allergic reactions have been reported in the literature so far (Table 1). Among them, 8 patients (14%) developed cardiac arrest (type IV) and the rest 49 patients (86%) developed type III allergic reactions. In the majority of cases, the anaphylactic reaction presented within the first 60 minutes after patent blue V administration. Prominent cutaneous manifestations such as widespread erythema, urticaria, or angioedema accompanied the severe anaphylactic shock. In some cases, a blue discoloration of the skin (blue wheals or blue urticaria) was surprisingly observed, due to the blue dye absorption. The initial anaphylactic shock resolved after

TABLE 1 Published cases of severe anaphylactic reactions to patent blue V in breast surgery. N/A, not available; ICU, intensive care unit

Year; Study	No of cases	Symptoms onset (min)	Cutaneous signs	Grade	ICU	Allergies
2001; Mullan	1	15	Widespread erythematous rash	III	YES	N/A
2004; Ingram	1	20	Lips, face and tongue edema	III	YES	Penicillin
2004; Wohrl	1	10	Urticaria	IV	N/A	NO
2005; Beenen	1	N/A	NO	III	NO	N/A
2006; Dewachter	1	45	Urticaria	III	N/A	Noramidopyrine
2008; Jeudy	3	20	Generalized urticaria	III	N/A	N/A
2008; Lanitis	1	10	NO	III	N/A	N/A
2008; Mertes	6	30 ± 6	Urticaria-Angioedema	III	N/A	Food & drug
2008; Thierrin	1	180	N/A	IV	YES	NO
2010; Barthelmes	5	5-40	Rash-Angioedema-Blue Wheals	III	2/5	N/A
2010; Alconchel	1	40	N/A	III	N/A	N/A
2010; Haque	3	25-40	Gross angioedema	III	YES	N/A
2010; Hunting	8	5-25	Generalized (blue) urticaria-Erythema	III: 7 IV: 1	1/8	N/A
2010; Lucas	3	7-20	Generalized Rash	III	N/A	N/A
2010; Rogler	1	20	NO	III	YES	NO
2012: Brenet	2	15-30	Urticaria	III	YES	NO
2012; Manson	4	20-50	Urticaria-Angioedema	III	YES	Wheat, ibuprofen
2012; Parvaiz	2	30	Severe blue urticaria	III	YES	N/A
2016; Lazaro	2	N/A	N/A	III: 1 IV: 1	N/A	N/A
2018; Harper	9	5-60	Nonspecified	III: 5 IV: 4	N/A	N/A
2018; Kumar	1	10	Discoloration of upper body	III	YES	N/A

intraoperative resuscitation, without ICU admission, for the two thirds of the patients. Finally, just a few patients reported a previous history of allergies.

Despite the minor risk (0.7%) of allergic reaction after patent blue administration, some safety concerns have been raised against this blue dye for colorimetric mapping in SLNB. Methylene blue has been proposed as a potential alternative to patent blue V, due to its comparable efficacy in SLN identification, its lower cost, and its decreased allergic stimulation.[13] Nevertheless, methylene blue injection for SLNB has been associated to skin reactions such as superficial ulceration or erythema at the injection site and skin necrosis when injection was intradermal, as well as severe capsular contracture around the implant. In addition, super paramagnetic iron oxide (SPIO) nanoparticles and indocyanine green fluorescence (ICG) have demonstrated adequate efficiency in SLN mapping in combination to a radio-isotope, but their safety has still to be proved.[14] Finally, the utilization of a radio-isotope alone without a blue dye is another proposed option with 84% SLN identification rate, but required advanced surgical experience.[15]

5 | CONCLUSION

Blue dyes have been routinely used for SLNB in breast surgery. However, anaphylactic reactions, and especially the severe ones (types III and IV), should be kept in mind as considerable adverse effects, although their incidence is low. Intraoperative anaphylactic shock triggered by patent blue V may threaten patient's life and no risk factors, like previous history of allergies or atopic predisposition, have been demonstrated so far. Nevertheless, blue dyes' low cost, increased efficacy, and low surgical complication rates make them an important tool in sentinel lymph node biopsy in breast surgery. Consequently, the advantages of blue dyes make their use justifiable, despite the low risk for anaphylactic reaction. The safety of patients could be further increased by intubation prior to blue dye injection, as our protocol described.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Maximos Frountzas: helped in data collection and writing. Charalampos Theodoropoulos: helped in data analysis and writing. Panagiotis Karathanasis: helped in data collection and writing. Christina Nikolaou: helped in data analysis. Constantinos G. Zografos: helped in data collection. Andreas Larentzakis: helped in study design. George C. Zografos: supervised the writing of the present paper. Nikolaos V. Michalopoulos: helped in study design.

ETHICAL APPROVAL

The present study was approved by the institutional research ethics committee and was performed according to the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

INFORMED CONSENT

Informed consent was obtained from all patients for being included in the study.

CONSENT TO PARTICIPATE

An informed consent was obtained.

CONSENT FOR PUBLICATION

An informed consent was obtained.

DATA AVAILABILITY STATEMENT

Data analyzed during the current study are available from the corresponding author on reasonable request.

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