



Angioedema to Patent Blue Dye in Breast Surgery: A Case Report and Review of Literatures

Hsuan-Cheng Wu^{1,2}, Jyh-Cherng Yu³, Lin-Chi Yi^{4,5}, Cheng-Shan Wu¹, Shu-Chuan Lin¹, Zhi-Fu Wu¹

¹Department of Anesthesiology, Tri-Service General Hospital, National Defense Medical Center; ²Division of Anesthesiology, Armed Forces Taoyuan General Hospital; ³Division of General Surgery, Tri-Service General Hospital, National Defense Medical Center; ⁴Division of Thoracic Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei; ⁵Division of Thoracic Surgery, Armed Forces Taoyuan General Hospital, Taoyuan, Taiwan

Patent blue is the safest and most widely available blue dye for lymphatic mapping during breast cancer and cervical cancer surgeries. This paper reports an anaphylactic reaction to patent blue used for lymphatic mapping during breast cancer surgery where the patient presented with angioedema with bilateral eyelid and upper airway edema. Anesthesiologists should be aware of the possibility of anaphylactic reactions to any drug or substance administered during surgery.

Keywords: Breast neoplasms, patent blue dye, modified radical mastectomy, anaphylaxis, angioedema

INTRODUCTION

When breast cancer metastasizes, it typically spreads to the first lymph node that its cancer cells reach; this node is referred to as the sentinel lymph node (SLN). The National Comprehensive Cancer Network has opined that SLN biopsy (SLNB) is the preferred method for dissection staging of the axillary lymph node in a breast cancer patient by an experienced surgeon.¹

The SLNB technique has not been internationally standardized, and the methods and materials used for the procedure vary among surgeons and institutions. The SLN can be located using intraparenchymal injection of blue dye, radiocolloid alone, or blue dye plus radiocolloid. Despite its proven benefit for patients, using blue dye for sentinel node mapping can cause severe complications. Patent blue dye (PBD) causes an adverse reaction in 0.9% of cases; symptoms may include erythema, hives, or cardiorespiratory arrest.² In this paper, we report an unusual case of angioedema where a patient undergoing breast cancer surgery presented with periorbital edema affecting the eyelids and upper airway edema after a PBD injection to map the SLN. We also present

a review of published studies on allergic reactions induced by PBD.

CASE PRESENTATION

A 57-year-old woman with a 24-mm hypoechoic lesion in the upper inner quadrant of the left breast and whose pathology showed ductal carcinoma *in situ* denied having any systemic disease or history of food or drug allergies. After being anesthetized with intravenous propofol (Fresfol 1%) by using Schneider's kinetic model of target controlled infusion (Fresenius Orchestra Primea; Fresenius Kabi AG, Bad Homburg, Germany) composed of propofol Ce 3–4 µg/mL,³⁻¹⁰ fentanyl, rocuronium, dexamethasone 5 mg, and ketorolac 30 mg, no specific skin lesion appeared on the face or anterior chest wall. Tracheal intubation was performed using a cuffed tube with an internal diameter of 6.5 mm and controlled mechanical ventilation with 400-mL tidal volume and a respiratory rate of 10 times/min. At 11:51 am, the 2 mL of 2.5% PBD was injected into the intraparenchymal subareolar region of the left breast. Quadrantectomy and

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Corresponding Author: Prof. Zhi-Fu Wu, Department of Anesthesiology, National Defense Medical Center, Tri-Service General Hospital, No. 325, Section 2, Chenggong Road, Neihu District 114, Taipei, Taiwan. Tel: +886-2-87923311 ext. 12852. Fax: +886-2-87927127. E-mail: aneswu@gmail.com

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left-side sentinel node dissection were performed. An ill-defined mass approximately 0.6 cm in size was observed in the left breast. The patient's blood pressure, heart rate, oxygen saturation, end-tidal carbon dioxide, and airway pressure were within the normal ranges perioperatively. After surgery, at 12:23 pm, the patient's bilateral upper eyelids were swollen, puffy, and blue [Figure 1a]; an anaphylactic reaction to PBD was suspected. The time interval between the injection and appearance of symptoms of an allergic reaction was approximately 32 min. After extubation, the patient had a persistent cough but normal oxygen saturation. She was transferred to the postanesthetic care unit (PACU), where she exhibited a persistent cough, itching of the throat, mild difficulty breathing, and multiple hives on the face [Figure 1b]. Because of suspected upper airway angioedema, a fibroscope of the larynx was performed, and diffuse edema of the vocal cords and epiglottis were observed [Figure 2], for which 30 mg of histamine-receptor- blocker diphenhydramine and 100 mg of hydrocortisone were prescribed and oxygen was supplied through a face mask. The anaphylactic reaction progressed to the bilateral lower limbs, which exhibited blue-colored urticaria [Figure 3a and b]. The patient was monitored in the PACU for 2 h. After her symptoms had improved, she was transferred to the ordinary ward. Her symptoms had resolved by the next morning and she was discharged.

DISCUSSION

Lymphatic mapping during breast surgery is a firmly established and minimally invasive technique for predicting a patient's axillary lymph node status. Many techniques have been used for lymphatic mapping, such as blue dye (Isosulfan blue, PBD V, or methylene blue), radiocolloid, or both in combination. Although PBD is regularly used for lymphatic mapping,¹¹ many reports have described its adverse effects. We performed a comprehensive computer-based literature search, searching the PubMed, Ovid, and Scopus databases for articles in English published up to July 2017, and used the following terms as medical subject headings: "blue dye," "anaphylaxis," and "SLN."

In 32 publications, we identified 63 patients who had experienced allergic reactions to PBD [Table 1]. Of these patients, 50, 12, and 1 had reactions during breast cancer surgery, melanoma surgery, and cervical cancer surgery, respectively. In most of the cases, the patient exhibited blue hives. Another 46 patients experienced hypotension and received inotropes, and three patients experienced cardiac arrest but were resuscitated without any sequelae. Seven articles calculated the incidence rate of adverse reactions [Table 2] and found that the overall rate of allergic reaction to PBD was 0.3%–0.9% and the grade III reaction rate was 0.06%–0.4%.^{2,12,13}



Figure 1: (a) Before extubation, the patient's bilateral upper eyelids were swollen, puffy, and blue, (b) multiple hives were observed on her face in the postanesthetic care unit

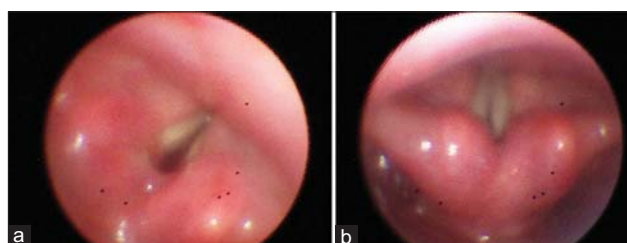


Figure 2: (a and b) Diffuse edema of the vocal cords and epiglottis were observed by using a fibroscope

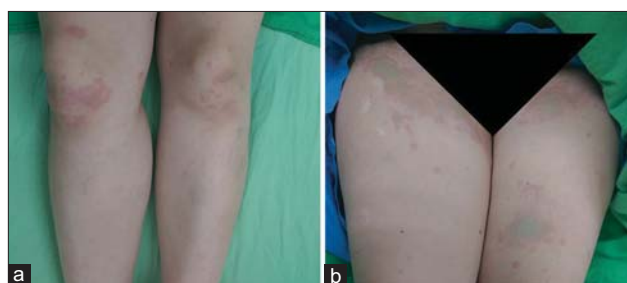


Figure 3: (a) Bilateral inguinal region (b) the patient's lower limbs had blue-colored urticaria

Anaphylaxis under anesthesia is uncommon, occurring in only 0.01% to 0.02% of patients, and neuromuscular-blocking drugs are the most common drug type related to anaphylaxis. Other causes of anaphylaxis are latex, antibiotics, opioids, nonsteroidal anti-inflammatory drugs, and local anesthetics. Understanding allergic reactions and how they occur during surgery is difficult. Anaphylaxis related to PBD is rare and symptoms include minor reactions such as urticaria, pruritus, erythema, generalized rash, and blue hives. The presence of blue hives is a clear diagnostic criterion of a reaction to PBD.² Severe reactions such as bronchial spasms and cardiac arrest are rare.^{23,28,38} In our case, the patient's bilateral upper eyelids

Table 1: Patent blue dye allergy reactions in 63 cases in 33 reports

Author, year	Procedure	Grade				Allergic test
		I	II	III	IV	
Aurich <i>et al.</i> , 2016 ¹²	Breast cancer			1		+
Maranhão <i>et al.</i> , 2016 ¹³	Breast cancer			1		NA
Boita <i>et al.</i> , 2015 ¹⁴	Breast cancer			1		+
Viegas <i>et al.</i> , 2015 ¹⁵	Breast cancer			1		+
Machado, 2013	Breast cancer			1		NA
Shyam <i>et al.</i> , 2013 ¹⁶	Melanoma	1				+
Parvaiz and Isgar, 2012 ¹⁷	Breast cancer	1	2			NA
Joshi <i>et al.</i> , 2012 ¹⁸	Breast cancer			1		NA
Manson <i>et al.</i> , 2012 ¹⁹	Breast cancer			4		+
Dang and Engel, 2012 ²⁰	Breast cancer			1		+
Robinson, 2011 ²¹	Breast cancer			5		+
Howard <i>et al.</i> , 2011 ²²	Melanoma			3		+
Telgenkamp <i>et al.</i> , 2010 ²³	Breast cancer				1*	+
Haque <i>et al.</i> , 2010 ²⁴	Breast cancer			6		+
Bricou <i>et al.</i> , 2009 ²⁵	Cervical cancer			1		+
Mertes <i>et al.</i> , 2008 ²⁶	Breast cancer	1	7	6		+
Lanitis <i>et al.</i> , 2008 ²⁷	Breast cancer			1		+
Thierrin <i>et al.</i> , 2008 ²⁸	Breast cancer				1*	NA
Cohen <i>et al.</i> , 2008 ²⁹	Melanoma		1	1		NA
Keller <i>et al.</i> , 2007 ³⁰	Melanoma			3		+
Weng <i>et al.</i> , 2007 ³¹	Breast cancer	1				NA
Mansouri <i>et al.</i> , 2006 ³²	Breast cancer		1			NA
Dewachter <i>et al.</i> , 2006 ³³	Breast cancer			1		+
van Zuuren <i>et al.</i> , 2005 ³⁴	Breast cancer			1		+
Olsha and Carmon, 2005 ³⁵	Breast cancer	1				NA
Bouman <i>et al.</i> , 2004 ³⁶	Breast cancer			1		NA
Ingram <i>et al.</i> , 2004 ³⁷	Breast cancer			1		NA
Wöhrl <i>et al.</i> , 2004 ³⁸	Melanoma				1*	+
Forschner <i>et al.</i> , 2003 ³⁹	Melanoma			1		+
Mullan <i>et al.</i> , 2001 ⁴⁰	Breast cancer	1		1		+
Woltsche-Kahr <i>et al.</i> , 2000 ⁴¹	Melanoma		1			+
Vrancken Peeters <i>et al.</i> , 2000 ⁴²	Breast cancer			1		+

*The patient had cardiac arrest; After advanced cardiac life support, the patient has return of spontaneous circulation; Grade I=Allergic skin reaction only; Grade II=Transient hypotension not requiring vasopressor support; Grade III=Transient hypotension requiring vasopressor support; Grade IV=Cardiorespiratory arrest and/or death. NA=Not available; +:skin prick test or intradermal test to PBV show positive

were swollen, puffy, and blue; which were the first indications that she had experienced an allergic reaction to PBD rather than shock. The patient also experienced an anaphylactic reaction that occurred in the upper airway and diffuse edema

Table 2: Incidences of adverse reactions to patent blue dye

Author, year	Procedure	Number of patients	Allergic reaction (%)	Grade III (%)	Allergic test	Type of article
Rauch <i>et al.</i> , 2016 ¹²	Breast cancer	2198	3/2198 (0.3)	2 (0.2)	NA	
Clarke <i>et al.</i> , 2013 ⁴⁵	Melanoma	1785	1/1785 (0.056)	0	NA	Letter
Brenet <i>et al.</i> , 2013 ⁴⁶	Breast cancer	1742	6/1742 (0.34)	2 (0.1)	+	
Rughani <i>et al.</i> , 2011 ⁴⁷	Melanoma	5527	2/5527 (0.04)	0	NA	
Hunting <i>et al.</i> , 2010 ⁴⁴	Breast cancer	1418	7/1418 (0.5)	5 (0.4)	+	
Barthelmes <i>et al.</i> , 2010 ²	Breast cancer	7917	68/7917 (0.9)	5 (0.06)	NA	
Beenen and de Roy van Zuidewijn, 2005 ⁴⁸	Breast cancer	371	4/371 (1.10)	1 (0.2)	NA	

Grade I=Allergic skin reaction only; Grade II=Transient hypotension not requiring vasopressor support; Grade III=Transient hypotension requiring vasopressor support; Grade IV=Cardiorespiratory arrest and/or death. NA=Not available; +: Skin prick test or intradermal test to PBV show positive

of the vocal cords and epiglottis; based on a careful review and to the best of our knowledge, our case is the first case report of angioedema in the upper airway as a reaction to PBD during breast surgery.

The aforementioned case reports have highlighted that rare adverse reactions may occur during general procedures when PBD is used and anesthesiologists and surgeons must be mindful of this possibility to achieve accurate diagnosis and manage any complications. First, surgeons should inform patients that PBD may exert an adverse effect and request written informed consent. However, routine preoperative screening for PBD allergy is unnecessary.⁴⁹ Second, if a patient has a history of allergic reaction to blue dye or the surgeon wants to completely avoid PBD-related adverse effects, radiocolloid can be used for an SLNB. The SLN identification rate for radiocolloid is higher than that when only blue dye is used in hospitals where radiotracers are available and staff members are experienced in using the radiocolloid SLNB technique.⁵⁰

If a surgeon must use PBD for lymphatic mapping, a preoperative prophylaxis such as glucocorticoid or diphenhydramine is recommended. Preoperative prophylaxis

has been found to reduce the severity but not the overall incidence of adverse reactions to blue dye.⁵¹ In our case, we administered 5 mg of dexamethasone, which may have decreased the severity of the adverse reaction.

In conclusion, anaphylactic reactions related to PBD are quite rare. Ours was the first case of PBD-induced upper airway edema complicated by mild respiratory distress during breast surgery. Anesthesiologists and surgeons should be aware of the potential for an adverse reaction to PBD when it is used for lymphatic mapping and must possess the ability and have access to the equipment available to perform an emergency resuscitation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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