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Anaphylactic Shock after Patent Blue Dye Injection

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Abstract **Case Report**

Intraoperative anaphylactic shock is an unusual complication. About a case report a severe anaphylactic reaction to Patent Blue (PB) dye used in sentinel node biopsy for lymphatic mapping during breast cancer surgery to stage the axilla, the authors discuss the mechanisms, principles of treatments, and prevention measures of this complication.

Keywords: Anaphylactic shock, sentinel lymph node, patent blue dye, treatment, prevention.

INTRODUCTION

The sentinel lymph node (SLN) procedure is used routinely for the staging of clinically node negative patients with early breast cancer. Two identification techniques exist: colorimetric and isotopic [1, 2]. These can be used alone or in combination. The combined method is associated with an increased identification rate. Furthermore, the combination of the two techniques reduced the time required for surgical training, since the surgical dissection follows the blue lymphatic channel and is therefore simpler. However, the blue dye may be the cause of immediate hypersensitivity reactions such as bluish urticaria, angioedema, bronchospasm or anaphylactic shock [1-4].

We report a case of anaphylactic shock secondary to patent blue dye during sentinel lymph node biopsy.

CASE REPORT

A 52-year-old woman was scheduled for elective surgery for a retro-areolar carcinoma measuring 10 mm of the left breast.

At the preoperative visit the patient measuring 168 cm and weighing 79 kg with a body mass index of 28 kg/m2. Her blood pressure was 123/65 mmHg, with a pulse rate of 73 beats/min. She had experienced tow previous operations without incident. No personnel or familial history of allergy was documented. On clinical examination, no palpable lesion was felt.

Preoperative examinations of the cardiovascular and respiratory systems were normal. Electrocardiography (ECG) was unremarkable. Laboratory tests including international normalized ratio, urea, creatinine, and blood glucose concentrations were normal.

She was premedicated the day before and the day of the surgery with alprazolam. The morning before the operation, she was given 20 Mbq technetium nanocolloid and scanned 10 min afterwards so that the sentinel node could be marked. Then, the patient was admitted in operative room where a standard monitoring including heart rate, arterial oxygen saturation (SpO2), and non invasive pression (NIP) has been installed. The initial parameters with a heart rate (HR) at 78 beats/min, NIP at 124/76 mmHg, and SpO2 at 99% have allowed induction of anesthesia with propofol (3 mg/kg), fentanyl (4 µg/ kg), and cisatracurium (0.15 mg/kg).

Tracheal intubation with a normal tube was successful realized with a standard laryngoscope. The patient was connected to the respirator and anesthesia was maintained with isoflurane (1%) in a mixture of nitrous oxide and oxygen (50%:50%). With ventilation by a tidal volume of 500 mL, and rate of 14 breaths/min, SpO2 was 97%, capnography [Endtidal CO2 (ETCO2)] was 36 mmHg.

The operating surgeon injected 2 ml of Patent Blue V 2.5% (calcium alpha-4-diethylaminophenyl-5-hydroxytoluene-2,4-disulphonate; Laboratoire Guerbet, France) in a subdermal fashion over the tumor. She underwent a wire-guided wide local excision.

Nearly at the end of the intervention, approximately 40 min after the dye was given, the patient had presented a generalized superficial and deep urticaria. This urticaria had the particularity of being bluish (Fig. 1). At the same time, a drop in arterial blood pressure (from 110/70 to 63/40 mmHg) and a slight decrease in end-tidal carbon dioxide concentration (from 32 to 26 mmHg) associated with tachycardia (from 70 to 120 beats/min) occurred. Her oxygen saturations remained constant throughout the procedure at 96%.

The surgery was finished quickly. Inhalator agent (isoflurane) was closed and oxygen fraction was increased to 100%. Pulmonary auscultation was normal and symmetric and there was no wheeze. Airway pressure (19 cmH2O) had not changed. Monitoring did not notice any changes in ECG. Diagnosis of anaphylactic shock was strongly suspected. A second peripheral venous catheter (16 gauge), and arterial catheter were placed. Fluid resuscitation (saline 0.9%) 500 mL per 500 mL (with a total of 1500 mL) and IV boluses of ephedrine (30 mg total) allowed only a slight improvement (NIP: 69/43 mmHg). Epinephrine boluses (100 µg to a total of 300 µg) were administered and relayed by continuous infusion (0.07 µg/ kg/min) via a central venous catheter. This therapeutic has stabilized the hemodynamic status (NIP: 106/60 mmHg and HR: 90 beats/min). A bolus of 100 mg of hydrocortisone was administered. Immediately after the reaction when the hemodynamic stability was restored, serum tryptase was measured and the patient was transferred to ICU.

Postoperative course was unremarkable with extubation 1 h later and a withdrawal of drugs 3 hours later. The patient was discharged home after 3 days of hospitalization without any residual effect.

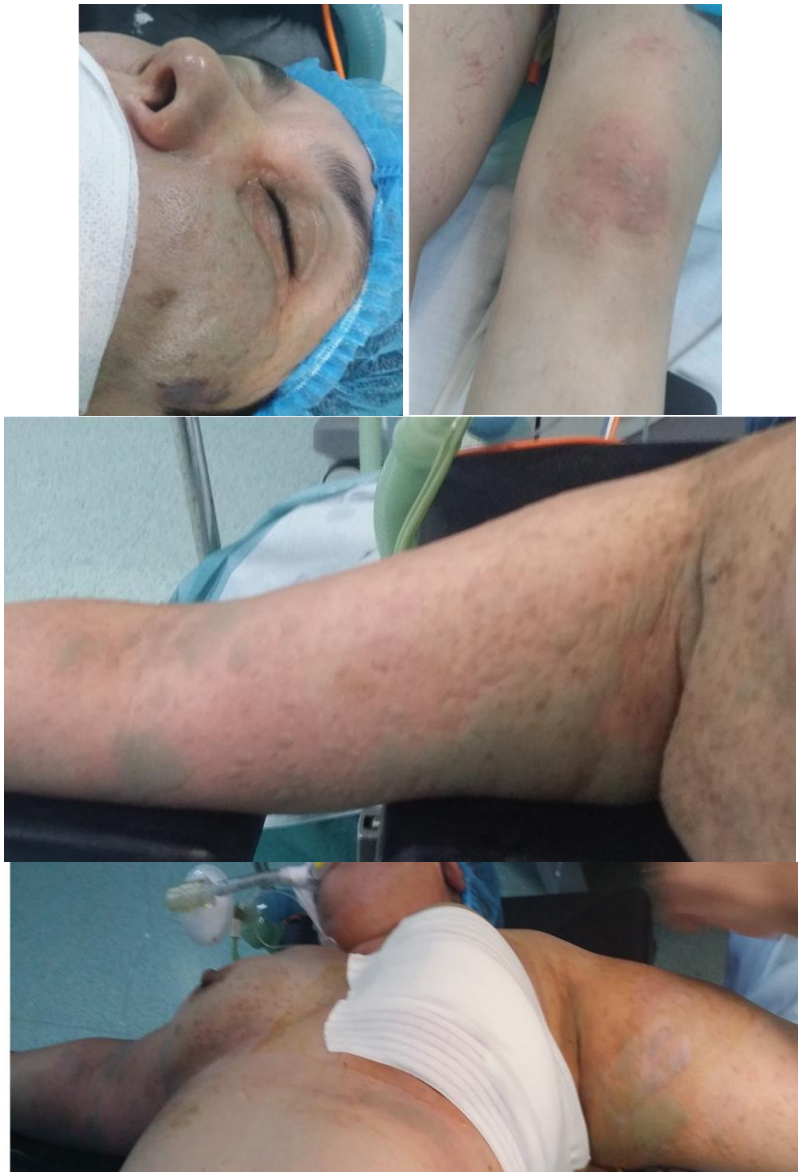

Fig-1: The pictures show body parts with the bluish urticaria. The urticaria were distributed all over the body

DISCUSSION

Anaphylaxis during anesthesia is uncommon. The estimated incidences of this complication vary between 1 in 5000 and 1 in 20,000[5] procedures with mortality from 3% to 6%[6]. All drugs and substances used during anesthesia and surgery may be implicated in these reactions. Muscle relaxants, antibiotics, and latex are most often involved [7]. We report a case of a lady who developed anaphylactic shock within 30 minutes of periareolar injection of the patent blue for sentinel node detection.

Two dyes are almost exclusively used for the sentinel node detection procedure in breast cancer [2] and to a lower degree in melanoma [4]: patent blue (PB) and its isomer isosulfan blue, and for which immediate hypersensitivity reactions similar to patent blue have been reported. PB is used in many textiles, paints, cosmetics, detergents, as well as in the food industry (certain chewing gums and chocolates) and in hand disinfection products. It is used in industry under the reference E 131 [4].

The first two cases reports of anaphylactic response to patent blue during lymphography were published by Kopp in 1966 [8]. Since then, several allergic reactions have been reported during lymphography and following topical use of the patent blue [4-13]. In the literature, the incidence of of patent blue anaphylaxis varies between 0.06 and 2.7% [2]. A large study of 7917 patients found an allergic reaction to the Patent Blue dye in only 72 patients (0.9%), Of these, 5 patients (0.06%) had similar allergic reactions to this case [8].

The underlying mechanism of an allergy to PB remains unclear. Some favour a classical IgE immune complex driven mechanism [9]. Wohrl detected PB and isosulfan blue specific IgE in a patient with near-fatal anaphylaxis to PB using ELISA (enzyme-linked immunosorbent assay) [10]. Widespread sensitization to PB could occur due to its common use as a food additive (E 131) and in textiles.

However, in the presence of preformed antibodies injection of PB should lead to an immediate immune response. Immediate anaphylaxis is uncommon [10]. In the literature, Most reactions to BP occur delayed by an average of 30 minutes supporting a non-immune complex mediated process of mast cell activation [9].

Several other adverse events are mentioned in the literature. The most observed ‘adverse event’ is the ashen look patients have after a treatment in which patent blue was injected [11]. This is believed to be the result of intracapillary circulating dye giving the skin a blue/white appearance instead of the normal pink. This look may be mistaken for anemia. It is witnessed in almost every patient [12] and therefore cannot be considered a real adverse event.

The circulating dye also influences the measurement of the oxygenation. As Momeni has shown, a fourfold number of patients (33%) have a significant decline in the measured oxygenation when using isosulphan blue during operation. The effect is a spurious reading of the pulse oximeter due to interference of the absorbed red light by the dye. When an arterial blood gas analysis is performed, no decline in real oxygenation is found. This effect can last up to 6 h [13].

For diagnosis and in our case, the late appearance of dermatological lesions (obvious blue wheals) and the hemodynamic instability has allowed to strongly suspect the diagnosis of anaphylactic shock secondary to the patent blue. The result of the serum tryptase dosage, which was 30 µg/l (N < 13.5 µg/l), confirmed the diagnosis of anaphylactic shock. However, in patients who develop hypotension only without other symptoms of anaphylaxis and patients who develop skin changes of uncertain allergic etiology warrant detailed investigation. For these patients it is important to exclude non-allergic reasons of hypotension (acute myocardial infarction, and hypovolemic shock) and investigate other potential allergens as this could have implications for future anaesthetics. For this reason, it is important to perform allergology tests on these patients six weeks after the episode. Prick tests and intradermal tests (IDR) for all drugs used during general anesthesia, antibiotics used as well as for latex and chlorhexidine [14, 15].

The treatment of anaphylactic shock during surgery is facilitated by the prior installation of monitoring, of vascular access and airway access if general anesthesia. This treatment consists of stopping administration of any medication, stopping momentary intervention, massive fluid resuscitation, and administration of vasopressor and corticosteroids. Fluid replacement should be assured by crystalloids. For vasopressor, epinephrine is the first-line treatment in most guidelines on perioperative management of anaphylaxis [14-16].

Glucocorticoids are often administered in the acute phase of anaphylactic shock, although their effects are delayed by several hours; a beneficial role has been suggested in preventing recurrence of the manifestations of anaphylaxis in the late phase especially in some cases, a biphasic anaphylactic reaction has been described, with hypotensive episodes occurring at 15 min and 2 h after blue dye injection [5-9]. This reaction must be recognized to manage the patient effectively in the post-operative period.

To date, there is no way to determine the risk of a reaction to blue dyes. There are no reports of adverse reactions to PB in patients with a food allergy or an allergy to E 121 [9]. Therefore, selective pre-operative skin testing of patients with a known allergic predisposition or food allergy does not appear to be beneficial and justifiable. For patients with a tendency to atopy or a history of allergy to other drugs such as penicillin, there is no evidence to suggest that they could have an anaphylactic reaction to blue dye and no cross-reactivity has been described between blue dye and any other drugs [9-11].

For Prevention, some surgical centers have tried to use only isotopes for sentinel node identification versus a combination of isotope and patent blue dye.10 Nevertheless, in approximately 10% of cases, the sentinel node was identified by the blue dye, even though it was not identified by the isotope [17].

The methylene blue dye has been used as alternative of Patent Blue dye. However, some skin reactions have been described with methylene blue. Stradling et al. and Thevarajah *et al*., described superficial ulceration or erythema at the dye injection site and some skin necrosis when injection was intradermal [18, 19]. In addition, there has been one report of severe capsular contracture around an implant following methylene blue injection [20]. It has been postulated that the toxic effects of methylene blue are due to the formation of aldehydes and a reduction in oxidation products, which leads to macrophage activation and an intense inflammatory response. Methylene blue also causes vasospasm due to the inhibition of nitric oxide synthesis [19]. Genuine allergic reactions have also been reported. Dewachter *et al*., reported a case of severe anaphylactic shock in response to intra-uterine injection of 1% methylene blue, which was used to determine tubal permeability that was later confirmed by cutaneous testing [21]. In addition, cross-reactivity between patent blue and methylene blue has been described [9].

Another alternative strategy using preoperative prophylaxis with corticosteroids and histamine antagonists has been reported to reduce the severity of reactions to isosulfan blue dye when they occur, but not the incidence of these reactions [11].

CONCLUSION

We wanted to highlight with this observation, that although Patent Blue dye is a powerful surgical tool, adverse reactions do occur and these can vary from mild to severe and some patients may suffer an anaphylactic shock which is a potentially lethal situation. Early recognition of the reaction and prompt treatment is the key to a successful outcome. All patients undergoing dye should give consent for adverse reactions.

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