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Case Report

Severe Anaphylaxis Associated with Isosulfan Blue Injection Used for Sentinel Node Detection: A First Case Report in Thai Breast Cancer Patients

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Abstract **Anaphylaxis is a severe systemic allergic reaction that generally manifests clinically as respiratory difficulty and circulatory collapse. It results from massive release of preformed mediators such as histamine from mast cell and basophils. Release of these mediators is caused by cellular binding of specific immunoglobulin-E antibodies. This release can produce a life threatening condition. There is a 1.5% reported incidence of allergic reaction to isosulfan blue dye, which has been used to localize the lymphatic system in breast surgery. Here, we report a 57-year-old Thai female presenting with severe anaphylaxis reaction from isosulfan blue injection for sentinel lymph node procedure in breast cancer. To the best of our knowledge, this is the first case report in Thailand. In addition, prophylaxis treatment for reducing severity of this condition is discussed.**

Keywords: Anaphylaxis, Breast cancer, Isosulfan blue dye, Sentinel node biopsy

Case Report

A 57-year-old woman presented with a left breast mass at the lower outer quadrant. Core biopsy revealed invasive ductal carcinoma with positive estrogen receptor, negative progesterone receptor, and strongly positive HER2 receptor by immunohistochemistry. She had no known drug allergies and no significant co-illness except for mild hypertension. Her medication consisted of atenolol and amlodipine. Her treatment plan was to perform a simple mastectomy with sentinel lymph node biopsy (SLNB) guided by isosulfan blue dye. On physical examination, she was noted to have a Mallampati class 2 airway with normal heart and lung examination. After induction of anesthesia, an endotracheal tube was placed without adverse reaction. Isosulfan blue (5 ml) was injected intraparenchymally around the tumor mass. Approximately 4 minutes after the injection, the systolic blood pressure declined from 120 to 60 mmHg and was unresponsive to ephedrine. Soon after, the ECG showed short runs of ventricular tachycardia during which the blood pressure could not be measured. Following that, there was sinus bradycardia 45/min, and the patient was resuscitated with intravenous atropine (0.6 mg), adrenaline (0.5 mg) and dexamethasone (5 mg). Dopamine was administered intravenously at a rate of 10 mcg/kg/min. The systolic blood pressure rose to 60 mmHg and the ECG revealed sinus tachycardia with elevated ST

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segments in the anterior chest leads. The patient was transferred to the ICU for further resuscitation and achieved clinical improvement within 3 hours. Cardiac catheterization showed no significant coronary stenosis. Levels of cardiac enzymes and cortisol were within normal limits. She was transferred out of the ICU the next day without sequelae. A modified radical mastectomy was successfully done 2 weeks later.

Discussion

Anaphylaxis during anesthesia is often a clinical diagnosis presenting, in decreasing frequency, with cardiovascular collapse, angioedema, erythema, bronchospasm (severe or transient), urticaria and/or rash, gastrointestinal symptoms, and pulmonary edema[1]. Cardiovascular collapse without other clinical signs or symptoms occurs in 10% of reported cases of anaphylaxis[2]. Both anaphylactic and anaphylactoid reactions may present with similar findings, because both are the result of massive mast cell histamine release. However, the mechanism of the reactions differs. Anaphylaxis is the result of covalent binding of IgE drug-specific antibody to mast cells with subsequent release of intracellular contents. The reaction may be self-perpetuating. Anaphylactoid reactions are also the result of mast cell histamine release, but are dose-related rather than self-perpetuating. Moreover, they are not IgE antibody dependent. Rapid release of these mediators in large quantities is responsible for the mucosal edema and capillary leakage that can lead to fatal shock and asphyxia[3].

A review of the literature[4-6] reports three methods that may be used to confirm the diagnosis of anaphylaxis: 1) biochemical evidence of mast cell histamine release (plasma histamine), 2) radioimmunoassay or enzyme-linked immunoassay for drug-specific IgE serum antibody, and 3) skin-prick testing of the patient with the suspected agent(s). To accurately measure plasma histamine levels, the patient specimen must be collected within 15 to 60 minutes of the event and stored in ice. Serum or plasma tryptase levels and urine methylhistamine specimens require collection within 3 hours of the event. Radioimmunoassay or enzyme-linked immunoassay antibody testing is not available for all drugs and is not always positive when serum tryptase levels are elevated and skin testing is reactive[4]. A skin-prick test allows either definite or probable identification of the causative agent in approximately 75% of cases[6]. The cause-effect relationship is often determined on the basis of clinical observations rather than laboratory tests[7,8].

Isosulfan blue, a rosaniline dye of the triphenylmethane type, is the 2,5-disulfonated isomer of patent blue dye. This dye, widely used during the course of SLNB, is the only dye of its type approved for lymphatic visualization by the Food and Drug Administration. After subcutaneous or intraparenchymal administration, isosulfan blue is selectively picked up by the lymphatic vessels, thus delineating the lymphatic system draining the area of injection. Fifty percent of isosulfan blue weakly binds to interstitial proteins, mostly albumin. Because interstitial protein is carried almost exclusively by lymphatics, visualization of SLNs may be due to a protein-binding phenomenon[8-10]. In our case, elevated serum tryptase was used to confirm the diagnosis of anaphylaxis. In addition, anesthetic agents used in patients who develop anaphylactic reactions, such as opiates, propofol, and isoflurane, are extremely rare causes of anaphylaxis during general anesthesia (1 in 60,000 cases)[11]. Thus, the relationship between the injection of isosulfan blue and the clinical response makes this agent the most probable cause.

The focus when anaphylaxis occurs during anesthesia should be on prompt and aggressive treatment in order to prevent an adverse outcome[7,8]. The first line of therapy involves the discontinuation of all anesthetic agents, administration of 100% oxygen, rapid infusion of large amounts of intravenous fluids, and prompt administration of epinephrine (0.1 to 0.3 mg intravenously given over 10 minutes). The second line of therapy includes H1-blockers (diphenhydramine hydrochloride 50 mg intravenously) and corticosteroids (methylprednisolone 125 mg intravenously). For refractory hypotension in patients receiving beta blockers, glucagon (1-mg ampoule) constitutes a third line of treatment[11].

After resolution of the acute episode, patients should be closely monitored for at least 24 hours as late reactions can be seen for several hours after surgery. This so-called biphasic anaphylactic reaction could be caused by a late systemic release of tissue depots of the antigen or by recruitment of late inflammatory mediators[10]. Therefore, when anaphylactic reactions occur during lymphatic mapping, we recommend close in-hospital observation for at least 24 hours after the

event. We monitored our patient for more than 24 hours, and there was no biphasic reaction. The incidence of allergic reaction to isosulfan blue dye ranges from 0.7% to 1.9%[7,12-14].

Longnecker et al.,[12] proposed premedication with histamine receptor (H1-and H2-) blockers (diphenhydramine and either cimetidine or ranitidine) before isosulfan blue dye administration to limit the reaction to the dye. Results of a surgical prospective clinical practice protocol from MD Anderson Cancer Center[10] showed a reduction in severe adverse reactions to blue dye in patients who received prophylaxis (0.5%), as compared to those without prophylaxis (8.3%). The protocol used a regimen composed of a glucocorticoid and histamine receptor blockers (100 mg of hydrocortisone or 4 mg of dexamethasone, 50 mg of diphenhydramine, and 20 mg of famotidine intravenously) just before or at induction of anesthesia in patients with breast carcinoma undergoing SLNB with isosulfan blue dye. Although the prophylactic regimen did not appear to reduce the incidence of adverse reactions significantly, the severity of reactions was decreased.

In our experience of more than 5,000 cases from year 2000 to the present, only one case developed severe anaphylactic reactions to isosulfan blue. Montgomery et al.,(15) reported 39 adverse reactions to isosulfan blue dye in a series of 2,392 patients (1.6%) undergoing mapping for breast carcinoma. Only nine cases of the adverse reactions were classified with Grade 3 severity. Neither study reported any deaths from dye injection.

Conclusion

In conclusion, SLNB is rapidly becoming the standard of care for identifying nodal metastasis in breast cancer. Nonetheless, anaphylactic reactions to isosulfan blue dye during the course of SLNB for breast cancer could have serious consequences, although their incidence is relatively low. As part of the informed consent process, patients should be informed of this potentially life-threatening allergic reaction. Surgeons performing lymphatic mapping must be aware and prepared to aggressively treat anaphylactic reactions that may result from this compound. However, routine prophylactic premedication with glucocorticoids and antihistamines is not recommended in Thai patients because this reaction is extremely rare.

Consent

Informed written consent for publication was obtained from the patient prior to collecting of data.

Conflicts of Interest

The authors declare that they have no conflict of interests.

Authors' Contributions

CO, and DS contributed to the collection of information and writing of the manuscript. DS contributed to the writing and final approval of the manuscript.

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บทคัดย่อ **อาการแพ้อย่างรุนแรงต่อการฉีดสารไอโซเซาฟานบลูในการทำการตรวจหาต่อมน้ำเหลืองเซนติเนลในการผ่าตัดมะเร็งเต้านม: รายงานผู้ป่วยรายแรกของประเทศไทย**

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**สาขาวิชาศัลยศาสตร์ศีรษะ คอและเต้านม ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล กรุงเทพมหานคร 10700*

อาการแพ้อย่างรุนแรงที่เกิดจากการแพ้สาร ทำให้มีปัญหาในการหายใจและความดันตกได้ ซึ่งเป็นผลจากการหลั่งสารฮีสตามีนจากมาสเซลล์และบาโซฟิลล์ โดยเฉพาะการเกิดกับการใช้สารไอโซเซาฟานบลู กับการผ่าตัดต่อมน้ำเหลืองเซนติเนลในผู้ป่วยมะเร็งเต้านม แม้มีเพียง 1.5% แต่ก็สามารถเกิดได้ และมีอันตรายถึงชีวิตถ้ารักษาได้ไม่ทันท่วงที บทนิพนธ์นี้ได้รายงานผู้ป่วยหญิงอายุ 57 ปีที่มารับการผ่าตัดมะเร็งเต้านมและใช้สารไอโซเซาฟานบลูและมีอาการแพ้สารตัวนี้อย่างรุนแรง นอกจากนี้ยังได้กล่าวถึงแนวทางการดูแลรักษาที่เหมาะสมเพื่อช่วยลดความรุนแรงของอาการแพ้ที่เกิดขึ้นจากสารนี้