CASE REPORT

Feeling blue, going green and finding other attractive alternatives: a case of biphasic anaphylaxis to patent blue and a literature review of alternative sentinel node localisation methods

Fahad Mujtaba Iqbal,¹ Abdul Basit,² Fathi Salem,³ Raghavan Vidya³

¹Department of Medicine, Keele University, Newcastle under Lyme, UK

²Keele University, Newcastle under Lyme, Staffordshire, UK
³County Hospital, Stafford, UK

Correspondence to

Fahad Mujtaba Iqbal,
fahad.iqbal@kclalumni.net

Accepted 20 November 2015

SUMMARY

Patent blue dye is used for sentinel lymph node localisation in order to stage the axilla in patients with breast cancer. Patent blue is one of the most common dyes used across the UK, however, the incidence of adverse effects seems to be increasing. This case highlights our experience of a biphasic anaphylactic reaction to patent blue dye, and we conduct a brief literature review of alternative and more novel methods to adequately visualise the lymphatics for sentinel lymph node biopsy.

BACKGROUND

Sentinel lymph node biopsy (SLNB) is a standard procedure for staging the axilla in patients with breast cancer. The SLN is normally identified with a subdermal injection of blue dyes, which weakly bind to serum albumin and form a complex.¹ This is picked up by regional afferent lymphatics to identify SLN with a bright blue colour.² Anaphylaxis to blue dyes has been previously reported but the incidence continues to rise as a result of the more frequent use of such dyes to visualise the lymphatics.^{2–3} Indeed, the reported incidence varies from 0.07% to 2.7%.⁴

We report a case with a biphasic anaphylactic response to patent blue with the secondary late phase reaction presenting mildly as a maculopapular rash. We also review the literature for alternative and more novel methods to adequately visualise the lymphatics for SLNB.

CASE PRESENTATION

A 35-year-old woman presented with a lump in the outer quadrant of her right breast. There was no family history of cancer. The patient had no significant medical history and reported no known allergies at the time of presentation.

Clinical examination revealed a 15×10 mm right breast lump, which was non-tender, firm and highly mobile. There was no skin tethering, nipple inversion or discharge. The patient's left breast appeared normal. She had no palpable cervical or axillary lymphadenopathy. Triple assessment (history/examination, imaging and histology) revealed a 16×9 mm lesion on ultrasound scan (USS) and a core needle biopsy of the lump showed a grade 1 invasive tubular carcinoma of the breast. USS of the axillary lymph nodes revealed no abnormal

morphology. A subsequent mammogram revealed a small area of microcalcification but, when biopsied, it was found to be benign.

Various surgical options were discussed in hopes of a curative treatment, and it was decided that a wide local excision (WLE) with a SLNB would be favourable, with additional antihormonal treatment (oestrogen receptor status positive) and radiotherapy, to reduce the chance of local recurrence, rather than a mastectomy.

A WLE under general anaesthesia was undertaken and the patient had 2 mL of 2.5% patent blue dye injected subdermally around the nipple areolar complex in the outer quadrant of the right breast, as part of the dual technique using also the radioisotope (technetium colloid, 99 m Tc) for localisation of the axillary SLNs. The breast was massaged for 2 min to adequately visualise the lymphatics. To this, the patient developed skin blisters, with blue wheals in the skin of her chest wall, and anaphylaxis, resulting in a decrease in her systolic blood pressure, which was appropriately dealt with using an injection of 100 mg hydrocortisone. Her oxygen saturations remained constant, at >95%, during this time.

The WLE was completed and two SLNs were removed. The histological examination of these lymph nodes was subsequently reported as negative for malignancy. The patient was admitted for observation to the high dependency unit and was discharged 24 h later. She was to be seen in the follow-up outpatient's clinic in 2 weeks' time.

Figure 1 A late phase reaction to patent blue dye resulting in a generalised maculopapular rash over the trunk. The wide local excision scar on the right breast can also be seen.

CrossMark

To cite: Iqbal FM, Basit A, Salem F, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-213107

Figure 2 A late phase reaction to patent blue dye resulting in a generalised maculopapular rash on the lower limb.

OUTCOME AND FOLLOW-UP

Following discharge, the patient was reviewed in the outpatient clinic. She had a generalised maculopapular rash that initially developed over the front of her trunk and later spread to both upper and lower limbs, persisting for 2 weeks following surgery, and that was thought to be a second reaction to the blue dye (figures 1 and 2). Consequently, a steroid cream and antihistamine were prescribed.

DISCUSSION

The Ring and Messmer scale is used for grading anaphylaxis severity (table 1).^{5 6} Although the first reaction in our case was grade 3, a mild secondary reaction (grade 1: urticaria and erythema) occurred. More serious complications, such as respiratory problems and cardiovascular collapse, have been reported.² In light of this, we admitted our patient for 24 h observation, as

an extended period of monitoring is required for possible treatment of a secondary severe anaphylactic reaction.

There are case reports suggesting that corticosteroids may prevent secondary reactions from occurring, but the evidence is inconsistent as some patients who received corticosteroids went on to experience a secondary reaction.^{2 7 8} In our case, the patient received hydrocortisone during the anaphylaxis and went on to develop an additional reaction. Indeed, further research into the usefulness of corticosteroids in preventing a secondary reaction is needed.

The detection of SLNs is thought to be improved with combination techniques; as a result, we used 99 m Tc alongside patent blue dye for SLN localisation. In 2007, a study (n=124) reported a higher concordance rate (91.9%, 95% CI 0.88% to 0.98%) when 99 m Tc and blue dye were used in conjunction for SLNB in patients with breast cancer (successful identification of SLNs with the combination technique was 98.4% (n=122), for blue dyes, 92.7% (n=115) and for 99 m Tc alone was 97.6% (n=121).⁹ However, a recent prospective study (n=42) concluded that dye alone is as effective as the combination technique.¹⁰ Both studies limited their inclusion criteria to low-grade tumours. Further research is required to determine the contribution of the combination technique in detecting SLNs versus dye and radiolabelled colloid alone in various-staged tumours.

Methylene blue use is an alternate to patent blue dye for SLNB. A prospective study (n=312) concluded that there were no differences in rates of axillary node detection using methylene blue and patent blue dyes (methylene blue group: 77.5% with dye alone and 94.2% with dye and radioisotope; patent blue group: 80.1% and 92.9%, respectively, $p>0.05$).¹¹ In addition, it has a lower reported incidence of anaphylaxis and does not share cross-reactivity with patent blue.¹² Interestingly, it is being considered for a new role in the treatment of distributive shock in anaphylaxis, perhaps through the nitric oxide-cyclic guanosine monophosphate pathway.¹³ This may suggest that, while anaphylaxis is reported with methylene blue dye, there may also be a preventative role. Further research is needed to understand both, the anaphylactic causing and relieving effects of the dye on the body, and whether it should be used preferentially to patent blue despite its greater incidence of tissue necrosis.¹⁴

Owing to the rise in blue dye anaphylaxis cases, alternative methods of SLN localisation are being sought out. One such method is the use of indocyanine green, which relies on molecular fluorescence generation: interaction with plasma proteins in the lymphovascular system and restoration of subatomic particles from excited to ground state results in fluorescent signal emission that can be visualised on a photodynamic eye camera.¹⁵ In 2014, a systematic review reported that indocyanine green was more accurate compared with blue dye for SLN

Table 1 Ring and Messmer scale of anaphylaxis severity^{5 6}

Grade 1	Grade 2	Grade 3	Grade 4
Cutaneous findings (erythema, urticarial, pruritus, angio-oedema)	Cutaneous findings Cardiovascular findings (hypotension, tachycardia) Respiratory findings (dyspnoea, wheeze) Gastrointestinal findings (nausea, vomiting, diarrhoea)	Cardiovascular findings (grade 2 and: cardiovascular collapse, profound hypotension, arrhythmia) Respiratory findings (grade 2 and: bronchospasm, hypoxia) Gastrointestinal findings (grade 2 and: incontinence) Neurological findings (confusion, reduced level of consciousness)	Cardiovascular findings (pulseless electrical activity, cardiac arrest)

identification (OR 18.37; 95% CI 8.83 to 39.10, $p < 0.0001$), with no significant difference noted between indocyanine green and radiocolloid (OR 0.81; 95% CI 0.03 to 24.29, $p = 0.02$).¹⁶ However, the number of studies considered was small and long-term data are needed with indocyanine green to appreciate any potential risks. Indeed, further use of indocyanine green is needed to reliably compare the incidence of potential adverse effects with blue dyes.

The use of superparamagnetic iron oxide nanoparticles is another novel technique for SLN assessment; these, after being injected in the peri-areolar, are detected with a handheld magnetometer. The SentiMAG multicentre trial (N=160) reported that the magnetic technique was non-inferior (defined as: 95% confidence limit <5% limit) compared to the standard technique (radioisotope with or without blue dye, dependent on local protocols). SLN identification was found to be 95% (n=152) with the standard technique versus 94.4% (n=151) with the magnetic technique, a difference of 0.6% (95% upper confidence limit 4.4%; 6.9% discordance).¹⁷ However, the study found that the magnetic technique did not always identify the same node as that identified by the standard technique, which could result in inaccurate staging; this may be due to direct competition between the dyes for the same SLNs. As a result, further randomised trials are needed to confirm non-inferiority.

In conclusion, while there are exciting novel alternatives to replace blue dyes for SLN localisation, the use of such new technologies is still at a premature stage with further randomised trials needed to prove their non-inferiority to the current technique. One should consider the possibility of a secondary late-phase reaction to blue dye if the initial administration resulted in a severe reaction, and one should remember that the grade of anaphylaxis severity to patent blue can vary from mild to severe. Initial management of anaphylaxis should include steroid administration—possibly along with adrenaline

—and the patient should be admitted to a high dependency unit for 24 h monitoring. Knowledge and careful vigilance of anaphylaxis should be exercised for appropriate treatment. Furthermore, all patients undergoing SLNB should be given informed consent for possible adverse reactions to patent blue dye. Using methylene blue dye as an alternative to patent blue dye may be an option until newer techniques have been adequately studied.

Twitter Follow Fahad Iqbal at @fmiqbal786

Contributors FMI drafted the manuscript. FS, AB and RV reviewed the manuscript and made amendments. AB was also the operating surgeon. All the authors reviewed and approved the final manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Montgomery LL, Thorne AC, Van Zee KJ, *et al*. Isosulfan blue dye reactions during sentinel lymph node mapping for breast cancer. *Anesth Analg* 2002;95:385–8.
- Liang MI, Carson WE III. Biphasic anaphylactic reaction to blue dye during sentinel lymph node biopsy. *World J Surg Oncol* 2008;6:79.
- Sprung J, Tully MJ, Ziser A. Anaphylactic reactions to isosulfan blue dye during sentinel node lymphadenectomy for breast cancer. *Anesth Analg* 2003;96:1051–3.
- Bézu C, Coutant C, Salengro A, *et al*. Anaphylactic response to blue dye during sentinel lymph node biopsy. *Surg Oncol* 2011;20:e55–9.
- Brown SGA. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* 2004;114:371–6.
- Dewachter P, Hepner DL. Anaphylaxis during radiological procedures and in the peri-operative setting. In: *Anaphylaxis and hypersensitivity reactions*. Springer, 2011:183–208.
- Popa VT, Lerner SA. Biphasic systemic anaphylactic reaction: three illustrative cases. *Ann Allergy* 1984;53:151–5.
- Douglas DM, Sukenick E, Andrade WP, *et al*. Biphasic systemic anaphylaxis: an inpatient and outpatient study. *J Allergy Clin Immunol* 1994;93:977–85.
- Kargozaran H, Shah M, Li Y, *et al*. Concordance of peritumoral Technetium 99m colloid and subareolar blue dye injection in breast cancer sentinel lymph node biopsy. *J Surg Res* 2007;143:126–9.
- Eser M, Kement M, Kaptanoglu L, *et al*. A prospective comparative study to assess the contribution of radioisotope tracer method to dye-only method in the detection of sentinel lymph node in breast cancer. *BMC Surg* 2013;13:13.
- Fattahi AS, Tavassoli A, Rohbakhshfar O, *et al*. Can methylene blue dye be used as an alternative to patent blue dye to find the sentinel lymph node in breast cancer surgery? *J Res Med Sci* 2014;19:918–22. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4274565/>
- van Zuuren E, Polderman MCA, Kuijken I. Anaphylaxis to patent blue during sentinel lymph node identification. *Contact Dermatitis* 2005;53:171.
- Jang DH, Nelson LS, Hoffman RS. Methylene blue for distributive shock: a potential new use of an old antidote. *J Med Toxicol* 2013;9:242–9.
- Reyes FJ, Noelck MB, Valentino C, *et al*. Complications of methylene blue dye in breast surgery: case reports and review of the literature. *J Cancer* 2011;2:20.
- Benson J. Indocyanine green fluorescence for sentinel lymph node detection in early breast cancer. *Ann Surg Oncol* 2015;1–3.
- Ahmed M, Purushotham AD, Douek M. Novel techniques for sentinel lymph node biopsy in breast cancer: a systematic review. *Lancet Oncol* 2014;15:e351–62.
- Douek M, Klaase J, Monypenny I, *et al*. Sentinel node biopsy using a magnetic tracer versus standard technique: the SentiMAG Multicentre Trial. *Ann Surg Oncol* 2014;21:1237–45.

Learning points

- ▶ Patients should be investigated for adverse effects to patent blue dye, particularly anaphylaxis.
- ▶ During patent blue dye administration the anaesthetist and the operating surgeon should observe for any signs of anaphylaxis.
- ▶ The grade of anaphylaxis severity to patent blue can vary significantly.
- ▶ The possibility of a secondary or biphasic response should be considered after the first anaphylactic reaction.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow