

Hypersensitivity reaction against patent blue during sentinel lymph node removal in three melanoma patients

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Abstract

Background: In order to identify the sentinel lymph node (SLN) in melanoma patients intradermal injection of a radiocolloid tracer and a blue dye are commonly used. Life-threatening side effects such as allergic reactions to the injected dye have been described. We report 3 cases with systemic allergic reactions.

Methods: Three patients suffering from systemic reactions such as hypotension and rash during SLN biopsy were tested for sensitisation against patent blue and methylene blue with skin prick, scratch, and intradermal test.

Results: All 3 patients showed positive skin tests to patent blue confirming allergic reaction to the injected dye. In addition, all patients showed positive skin tests with methylene blue indicating immunologic cross-reactivity between patent blue and methylene blue.

Conclusions: Although allergic reactions to blue dye during SLN biopsy are rare, they may be life threatening. It is important that the attending anesthetist is aware of this. © 2007 Excerpta Medica Inc. All rights reserved.

Keywords: Sentinel lymph node dissection; Melanoma; Allergy; Patent blue; Hypersensitivity reaction

The sentinel lymph node, the first node to drain lymphatic spread from a tumor, is usually located by preoperative lymphoscintigraphy and patent blue injection. The sentinel lymph node (SLN) biopsy is a widely accepted staging method for patients with malignant melanoma. Only few complications have so far been described, and this method is therefore considered to be safe.

First described in 1977 in 80 patients with penile cancer [1], the SLN detection is currently used for the evaluation of the management of various malignancies like melanoma, breast cancer, high-risk endometrial carcinomas, Hurthle cell thyroid neoplasm, non-small-cell lung cancers, colon cancer, squamous-cell carcinomas of the head and neck, and squamous-cell cancer of the vulva [2]. There are 2 different ways of identifying the SLN: by intraoperative gamma-probe detection after radiocolloid injection [3] or by visual identification after injection of a dye, such as patent blue [4]. Combining both methods increases the success rate of

harvesting the SLN to 99% compared with radioactive mapping alone and dye injection alone with 94% and 82%, respectively [5]. In a retrospective study, we analyzed the data of 3 patients who suffered systemic reaction during SLN biopsy and who revealed a positive sensitization to the injected blue dye during our routine allergological screening.

Patient 1 is a 35-year-old woman with a history of 2 malignant melanomas since 2002. In September 2002, a SLN biopsy was performed under general anesthesia because of a malignant melanoma (type SSM, Breslow 0.6 mm, Clark III) on the left knee. During this procedure, the patient had initially experienced pruritus, urticaria, and angioedema, but no further evaluation of this episode was done as the symptoms were not recognized as an allergy to patent blue. In February 2004, a second melanoma (Breslow 0.6 mm, Clark-Level II) was diagnosed in the paraumbilical region, and SLN biopsy was again performed. Under general anesthesia, the patient received again 4 mL patent blue intradermally around the scar of the previously removed melanoma. Thirty minutes after the injection, the patient

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became hypotensive and developed angioedema and urticaria. No bronchospasm or other allergic skin symptoms were noted. Both episodes were treated with intravenous methylprednisolone (40 mg) and intravenous histamine receptor blockers (clemastine and ranitidine). Skin tests (skin prick test and intradermal test) with both patent blue and methylene blue were positive (Figs. 1A and B). Skin tests were negative in 5 control patients tested with blue dye. Skin prick test was performed by using 2.5% patent blue (Patent blue V, E131, 25 mg/mL; Guerbe Inc, Zurich, Switzerland) as previously described [6]. Patent blue V (2.5%) diluted 1:100 was used for the intradermal test [7].

Patient 2 is a 70-year-old woman with a history of a malignant melanoma (Breslow 1.4 mm, Clark level IV) on the left lower limb. In March 2004, a SLN biopsy was performed by using patent blue under general anesthesia. During surgery, the patient developed tachycardia, hypotension (50 mm Hg), generalized urticaria, and angioedema of the face. The patient was treated with intravenous clemastine (2 mg), methylprednisolone (125 mg), and epinephrine (0.1 mg). According to the patient's history, it was the first exposure to patent blue. The allergological workup revealed

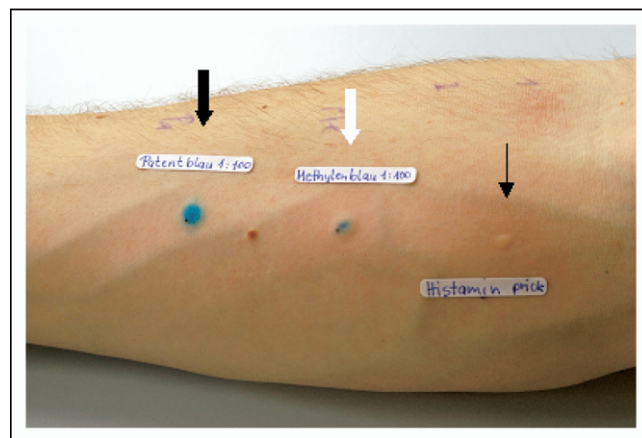


Fig. 2. Skin tests in patient 3. Positive prick test to patent blue (black arrow) and methylene blue (white arrow), control prick test with histamine (thin arrow).

no other drug allergy. Skin tests with all drugs used during the procedure were negative with the exception of a positive prick test reaction to patent blue (2.5%, performed as described earlier).

Patient 3 is a 26-year-old man with a history of a malignant melanoma on the upper back left (Breslow 1.2 mm, Clark III). In March 2005, a SLN biopsy was performed by using patent blue under general anesthesia. Ten minutes after injection of 4 mL patent blue, the patient developed a generalized erythema with urticaria and slightly swollen upper lips. After repeated injections of an H1-blocker (clemastine), all symptoms disappeared and no other complications were noted. Skin scratch tests with both patent blue and methylene blue were positive (Fig. 2). A scratch test was performed as described previously [8] by using 2.5% patent blue V.

Patent blue (alphazurine 2G) is a rosaniline dye of the triphenylmethane type. It is selectively picked up by the lymphatic vessels, and approximately 50% of the total injected volume binds to serum proteins. So far, only single case reports of allergic adverse reactions to this dye have been described. The symptoms vary from mild allergic reaction to anaphylaxis with cardiovascular collapse and even death [9–12]. One case was shown to be biphasic, which indicates that such patients should at least be under surveillance for additional 12 hours [13]. The time interval from injection to begin of the symptoms is usually 15 to 30 minutes.

Because of the clinical course and the positive results of the skin tests an immediate immunoglobulin (Ig) E-mediated reaction is most likely in our patients. Furthermore, a negative lymphocyte proliferation test with the injected dye as seen in 1 patient supports the notion that a T-cell-mediated immune response is not involved. The lymphocyte proliferation test was performed as previously described [14]. Briefly, 200,000 peripheral mononuclear cells were incubated with different concentrations of patent blue. Proliferation was assessed by measuring 3H-thymidine incorporation overnight in a 6-day culture.

In this retrospective analysis, it is difficult to determine the frequency of this allergic reaction to patent blue. In the

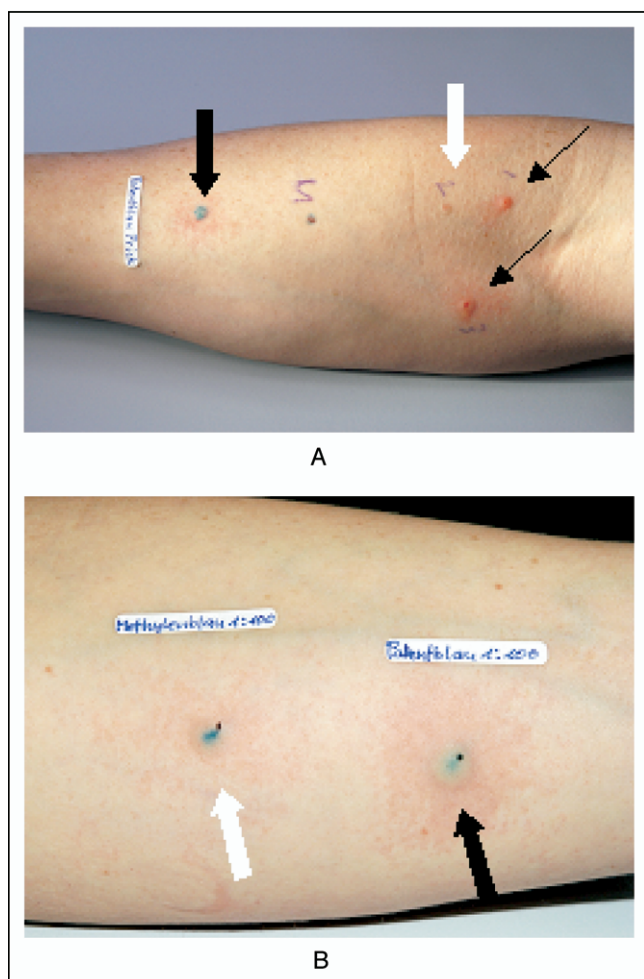


Fig. 1. Skin tests in patient 1. (A) Positive prick test to patent blue (black arrow), positive control with codeine and histamine (thin arrows) and negative control with saline (white arrow). (B) Positive intradermal test to patent blue (black arrow) and methylene blue (white arrow).

same time period, an estimated number of 370 SLN dissections were performed. This gives an estimated frequency of 0.8% allergic reaction against patent blue, a similar frequency as previously reported with the dye isosulfan blue by Leong et al [13]. The larger study of the Sunbelt Melanoma Trial Study Group, however, reported no complications related to injection of blue dye in 2120 patients [15], and the International Multicenter Trial reported an incidence of 0.17% (2 of 1173) allergic reactions (all blue hives) with no anaphylaxis [16]. It is difficult to find factors responsible for this difference in the incidence of severe allergic reactions against those blue dyes. Leong et al [13] reported about 1% anaphylactic reactions against isosulfan blue, whereas the in the Sunbelt Melanoma Trial [15] using the same amount (1–5 mL) of the same dye reported no allergic reactions. A similar situation is found in studies using patent blue. In our clinic, about 4 mL patent blue is injected leading to about 1% anaphylactic reactions, whereas the International Multicenter Trial [16] using 1 to 2 mL patent blue or isosulfan blue reported no systemic allergic reactions. Further studies are required to see if a lower dose of patent blue reduces the frequency and severity of allergic reactions to this dye.

Although there is no clear biochemical evidence for cross-reactivity between patent blue and methylene blue, the positive skin tests in previously not exposed individuals suggests that preformed IgE antibodies (originally directed to another antigen) causes the allergic reaction at first contact with patent blue. Wohrl et al [17] could detect specific IgE to patent blue, cross-reacting with isosulfan blue. This author discusses that different colors encountered in daily life such as food coloring E131 lead to sensitization.

A careful allergological evaluation is required before reexposure of these patients to any blue dye. Because reactions may occur without a previous history, all doctors involved in SLN biopsies should be aware of this rare but possibly life-threatening adverse effect. It is important that patients with known sensitization against a blue dye are informed about the danger of a second exposure, and they should be given a medical-alert tag.

A recent study analyzing isosulfan blue dye allergy during SLN dissection for breast cancer indicates that prophylaxis reduces the severity but not the frequency of these allergic reactions [18]. Based on the low frequency of those events, a general prophylaxis is, however, not performed at our clinic. Further studies are required to confirm a benefit

of a prophylaxis. It is, however, important that the anaesthetist is aware of this possible side effect and that the necessary emergency equipment including vasopressors is available.

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