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References

- [1] Holgate S, Casale T, Wenzel S, Bousquet J, Deniz Y, Reisner C. The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation. *J Allergy Clin Immunol*. 2005;115:459–465.
- [2] Novartis, Inc. Xolair (omalizumab) [product insert]. Dorval, Quebec, Canada; 2011.
- [3] US Food and Drug Administration. Center for Biologics Evaluation and Research. BLA STN 103976/0, briefing document on safety (Genentech Inc). Rockville, MD: Department of Health and Human Services; 2003.
- [4] Pilette C, Coppens N, Houssiau FA, Rodenstein DO. Severe serum sickness-like syndrome after omalizumab therapy for asthma. *J Allergy Clin Immunol*. 2007;120:972–973.
- [5] Dreyfus DH, Randolph CC. Characterization of an anaphylactoid reaction to omalizumab. *Ann Allergy Asthma Immunol*. 2006;96:624–627.
- [6] US Food and Drug Administration. FDA proposes to strengthen label warning for Xolair [news release]. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108850.htm>. Published 2007. Accessed February 17, 2015.
- [7] Cox L, Platts-Mills TAE, Finegold I, Schwartz LB, Simons ER, Wallace DV. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. *J Allergy Clin Immunol*. 2007;120:1373–1377.
- [8] Cox L, Lieberman P, Wallace D, et al. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology Omalizumab-Associated Anaphylaxis Joint Task Force follow-up report. *J Allergy Clin Immunol*. 2011;128:210–212.
- [9] Birnbaum ZW, Sirken MG. Design of sample surveys to estimate the prevalence of rare diseases: three unbiased estimates. *Vital Health Stat*. 1965;11:1–8.
- [10] Committee for Orphan Medicinal Products. Points to consider on the calculation and reporting of the prevalence of a condition for orphan designation. European Agency for the Evaluation of Medicinal Products. COMP/436/01. www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500003773. Published March 26, 2002.

Basophil activation test in the diagnosis of patent blue V anaphylaxis



Hypersensitivity reactions to subcutaneous injections of patent blue V (PBV) are well recognized, with an estimated incidence ranging from 1% to 2% when all reactions are considered and severe reactions being observed in 0.2% to 1.1% of cases.^{1,2} PBV, also known as E131, acid blue 3, and disulfide blue, belongs to the group of triarylmethane synthetic dyes.³ Since the 1960s, these dyes have been used in different medical procedures and particularly in intraoperative lymphatic mapping and sentinel lymphadenectomy.¹ In a recent multicenter retrospective study, patent blue dye was reported as causing anaphylaxis during general anesthesia in 5% to 6% of cases.⁴ Blue dyes also are used as excipients in food. Hypersensitivity reactions have been reported only in association with parental administration and never after blue dye ingestion as a food excipient. In many reported cases, positive skin prick test (SPT; or intradermal test) reactions and increased concentration of serum tryptase³ have supported the hypothesis of an IgE-mediated reaction. In fact, Wöhrl et al⁵ demonstrated the presence of specific IgE to PBV (and to isosulfan blue, with which antibodies to patent blue strongly cross-react) using an enzyme-linked immunosorbent assay.

In a few cases, the basophil activation test (BAT) has been reported to yield contrasting results. In particular, Viegas et al⁶ reported a negative BAT reaction when performed 49 months after a reaction, whereas Johansson et al⁷ reported positive BAT reactions in 5 of 9 patients with PBV anaphylaxis who underwent testing 13 to 92 months after anaphylaxis. Timing since the drug reaction might influence the performance of the test.

This report describes a case of a positive BAT result 1 month after severe anaphylaxis owing to patent blue allergy.

A 66-year-old woman with no personal or family history of atopy was referred to our outpatient clinic for suspected drug reactions. During the mapping and excision of sentinel lymph nodes for breast cancer, she received levobupivacaine and 2 vials of PBV. After 5 minutes, she developed foot itching, diffuse erythema, and severe hypotension (systolic blood pressure 40 mmHg). Epinephrine, fluid, and methylprednisolone were immediately administered, the surgical procedure was abandoned, and the patient was transferred to the intensive care unit, where she recovered completely. Her tryptase level was elevated to 30.8 µg/L during the acute phase of the reaction and decreased to a normal value (6.8 µg/L) 24 hours afterward. One month later, the patient was referred to our center for allergologic evaluation.

The SPTs and specific IgE testing for common inhalant allergens, including latex, were performed, with negative results. Local anesthetic allergy was excluded by SPTs (1:1) and intradermal tests (1:10) with lidocaine, mepivacaine, bupivacaine, and levobupivacaine. Subcutaneous provocation tests with mepivacaine and levobupivacaine, performed on 2 different days, did not provoke any reaction. An SPT reaction with PBV (25 mg/mL) was positive at a 1:10 dilution, with a wheal size of 6 mm. To find an alternative safe dye, an SPT and an intradermal test (1:1,000 and 1:100 dilutions, respectively) with methylene blue (MB) also were performed, with negative results.

The BAT was performed with the causative agent (PBV) and MB in the patient and in 3 healthy control subjects. The details of the BAT procedure have been reported previously.⁸ Briefly, 100-µL aliquots of endotoxin-free, heparinized whole blood were stimulated with dilution buffer as a negative control, anti-IgE (10 µg/mL; Pharmingen, BD Biosciences, San Jose, California) as a positive control, or serial dilutions (pure stimulatory concentration of 25 mg/mL; 1:10, 1:100, and 1:1,000 dilutions) of PBV. Basophils were gated as low side scatter per IgE⁺ cells. Upregulation of CD63 and CD203c was measured as an activation marker (Fig 1).

Figure 1 shows the upregulation of CD63 and CD203c in the BAT experiments. PBV induced dose-dependent upregulation of CD63 and CD203c, whereas no activation was detected after stimulation with MB. Expression of CD63 and CD203c on basophils from the 3 healthy control individuals remained unchanged.

After the BAT investigation, the patient underwent surgery with safe and successful use of MB for the mapping of sentinel lymph nodes.

A flow cytometry-assisted BAT has been used in the diagnosis of drug immediate hypersensitivity. The BAT is more expensive and technically challenging than conventional in vitro and in vivo tests, but it has the advantage of simultaneously assessing multiple drug responses, without the risk of endangering the health of the patient.

The performance of the test depends on the timing since the drug reaction. Laysen et al⁸ recommended an interval from the drug reaction to the BAT of 1 to 12 months. The negative BAT result reported by Viegas et al⁶ in a patient with PVB anaphylaxis might be explained by the relatively long interval (49 months) since the reaction. In the present case, the short (1 month) interval allowed us to diagnose hypersensitivity to PVB and to exclude cross-sensitivity to MB, giving the patient the opportunity to undergo the planned surgery.⁴

In summary, this case report illustrates the usefulness of the BAT for investigating a patient with intraoperative anaphylaxis to find the culprit drug and a safe alternative drug.

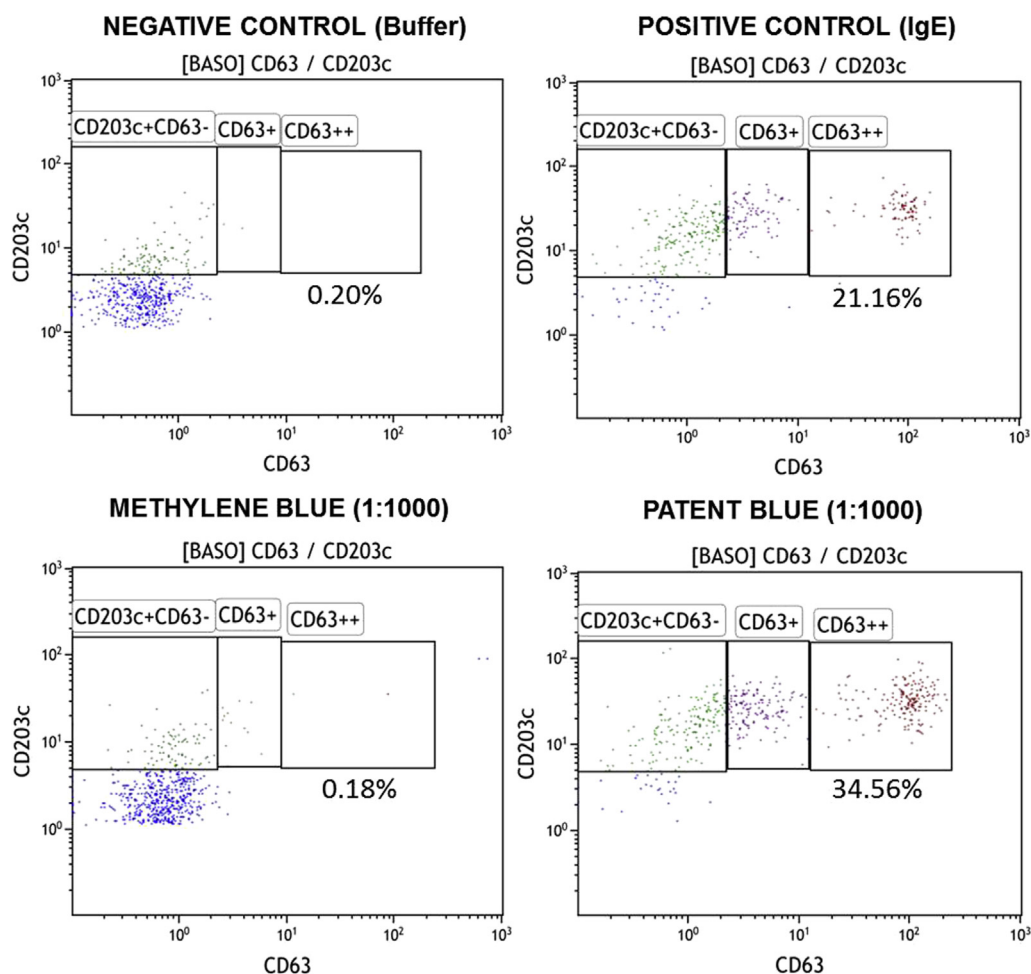


Figure 1. Basophil activation test. Scattered dot plots after stimulation with buffer (negative control, upper left), anti-IgE (positive control, upper right), methylene blue (lower left), and patent blue V (lower right), showing upregulation of CD63 on the basophil membrane (BASO).

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References

- [1] Mertes PM, Malinovsky JM, Mouton-Faivre C, et al. Anaphylaxis to dyes during the perioperative period: reports of 14 clinical cases. *J Allergy Clin Immunol*. 2008;122:348–352.
- [2] Scherer K, Studer W, Figueiredo V, Bircher AJ. Anaphylaxis to isosulfan blue and cross-reactivity to patent blue V: case report and review of the nomenclature of vital blue dyes. *Ann Allergy Asthma Immunol*. 2006;96:497–500.
- [3] Haque RA, Wagner A, Whisken JA, Nasser SM, Ewan PW. Anaphylaxis to patent blue V: a case series and proposed diagnostic protocol. *Allergy*. 2010;65:396–400.
- [4] Krishna MT, York M, Chin T, et al. Multi-centre retrospective analysis of anaphylaxis during general anaesthesia in the United Kingdom: aetiology and diagnostic performance of acute serum tryptase. *Clin Exp Immunol*. 2014;178:399–404.
- [5] Wöhrl S, Focke M, Hinterhuber G, Stingl G, Binder M. Near-fatal anaphylaxis to patent blue V. *Br J Dermatol*. 2004;150:1037–1038.
- [6] Viegas LP, Lopes A, Campos-Melo A, Ferreira MB, Barbosa MP. Patent blue anaphylaxis: case report. *J Allergy Clin Immunol Pract*. 2015;3:112–113.
- [7] Johansson SG, Nopp A, Oman H, Stahl-Skov P, Hunting AS, Guttormsen AB. Anaphylaxis to patent blue V. II. A unique IgE-mediated reaction. *Allergy*. 2010;65:124–129.
- [8] Leysen J, Sabato V, Verweij MM, et al. The basophil activation test in the diagnosis of immediate drug hypersensitivity. *Expert Rev Clin Immunol*. 2011;7:349–355.

Localized facial cold urticaria

Cold urticaria is a subclass of physical urticaria that is characterized by pruritic hives and/or angioedema due to cutaneous mast cell activation after cold exposure. It typically affects young adults, with males and females being affected equally, involves any part of the body exposed to cold, and is diagnosed by an ice cube test. On

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the other hand, idiopathic localized cold urticaria (LCU) is rare in both the pediatric and adult populations. LCU differs from cold urticaria in that the hives occur only at limited skin sites rather than any area on the body that is exposed to cold.¹ It can be either idiopathic or secondary to illness, food, insect sting, or allergen immunotherapy.^{2–4} We present a case of idiopathic LCU and review other similar cases.

