

Concurrent immunoglobulin E–mediated neuromuscular blocking agent allergy in systemic mastocytosis



Mastocytosis is a rare clinical condition characterized by an abnormal increase in tissue mast cells, which can be limited to the skin (cutaneous mastocytosis) or infiltrate the bone marrow and other organs with or without skin involvement (systemic mastocytosis). Systemic mastocytosis (SM) is reported primarily in adulthood, where indolent SM is the most common form. We report an unusual case consistent with immunoglobulin E (IgE)–mediated neuromuscular blocking agent (NMBA) allergy evidenced in a patient with previously unsuspected mastocytosis.

A 62-year-old woman was scheduled for appendectomy. Her medical history included a previous uneventful colonoscopy under anesthesia. In the current case, anesthesia was induced with sufentanil, propofol, and rocuronium. Tracheal intubation was performed and mechanical ventilation initiated. Two to three minutes after administration of rocuronium, the patient developed generalized erythema with cardiovascular collapse (from 134/59 to 55/28 mm Hg), arterial oxygen desaturation (from 99% to 90%), hypocapnia (end-tidal CO₂ of 23 mm Hg), and tachycardia (from 79 to 130 beats/minute). No bronchospasm was observed. Cardiovascular signs subsided in less than 5 minutes after intravenous titrated epinephrine (cumulative dose up to 500 µg) along with fluid therapy with crystalloids (0.9% saline solution, 500 mL). Anesthesia was maintained with sufentanil and desflurane. Surgery was completed. Neuromuscular blockade was reversed with sugammadex. The postoperative course remained uneventful.

Plasma tryptase (FEIA, ImmunoCAP Phadia 250, Thermo Fisher Scientific, Saint Quentin en Yvelines, France) levels measured 40 and 120 minutes after the onset of the reaction were greater than 200 and 151 µg/L, respectively ($n < 13$). Skin testing was performed 3 months later.¹ A prick-test to rocuronium (10 mg/mL) was strongly positive. Prick-tests also evidenced cross-sensitization to succinylcholine and vecuronium. Prick-test and intradermal tests to atracurium and cis-atracurium, up to the maximal recommended concentrations, remained negative, as well as skin tests with propofol and sufentanil. Rocuronium and cross-reactive NMBAs were prohibited for subsequent anesthetics.

Immunoglobulin E (IgE)–mediated rocuronium allergy was diagnosed according to the timing between rocuronium administration and the onset of symptoms, the clinical presentation along with tryptase levels and skin tests results.²

Additionally, skin examination showed small and monomorphic reddish brown hyperpigmented maculopapular lesions consistent with urticaria pigmentosa skin lesions, disseminated over the trunk, abdomen, and lower limbs. The facial skin, upper limbs, palms, and soles were spared. Skin lesions typically show a wheal-and-flare response on rubbing, consistent with a Darier's sign.³ On further detailed clinical review, skin lesions started to develop during late adolescence. No other symptoms were reported. Baseline tryptase level was strongly increased (86 µg/L) at the time of skin testing. A KIT D816V mutation was subsequently detected in lesional skin tissue³ by complementary DNA direct sequencing and after BsmAI restriction enzyme digestion for codon 816. A colonoscopy was performed, with random biopsies.⁴ Immunohistochemical staining with CD117 (c-KIT) showed a diffuse infiltration of mast cells (up to 15 mast cells in aggregate) within the lamina propria (Fig 1).

The diagnosis of SM could be established, because the World Health Organization diagnostic criteria were fulfilled.⁵ In addition, because osteoporosis is the most prevalent bone manifestation in SM,⁶ bone mineral density was measured, and it showed lumbar osteoporosis (T score: -3.0) along with bilateral femoral neck osteopenia (T score: -1.3). We suggested a complete staging, including a bone marrow biopsy, to our patient, but she refused to be referred for hematological follow-up.

Thus, this patient had both Ig-E mediated rocuronium allergy and SM. This latter condition remained unsuspected until the patient was referred for allergological assessment. More than 80% of adults with mastocytosis carry D816V mutation in the KIT gene,³ which induces constitutive mast cell activation. Mastocytosis thus may be involved in perioperative immediate hypersensitivity. The perioperative risk attributed to the disease itself appears to be overstated in the literature, however.

Various nonspecific triggers including histamine-releasing agents (atracurium, mivacurium, vancomycin) and other mechanical or physical factors may be involved.^{5,7} The use of preoperative H₁- and H₂-receptor antagonists and/or corticosteroids is usually recommended in patients with mastocytosis but has never been evaluated in placebo-controlled trials.^{5,7} The best way to avoid mast cell degranulation is to avoid known triggers.^{5,7}

After skin testing, only benzyloisoquinoline NMBAs (atracurium and cis-atracurium) remained negative. Because atracurium is a histamine-releasing agent usually not recommended in mastocytosis,^{7,8} cis-atracurium was preferentially suggested for further anesthetics. In contrast, mastocytosis is not a risk factor of IgE-mediated drug-allergy.^{7,8} Evidence for an association appears to be limited.⁵ Very few data are available on increased baseline tryptase and drug hypersensitivity severity, in contrast to *Hymenoptera* venom allergy where SM has been identified as a risk factor for fatal IgE-mediated anaphylaxis.⁵ In the current case, the magnitude of cardiovascular disturbances was similar to that occurring

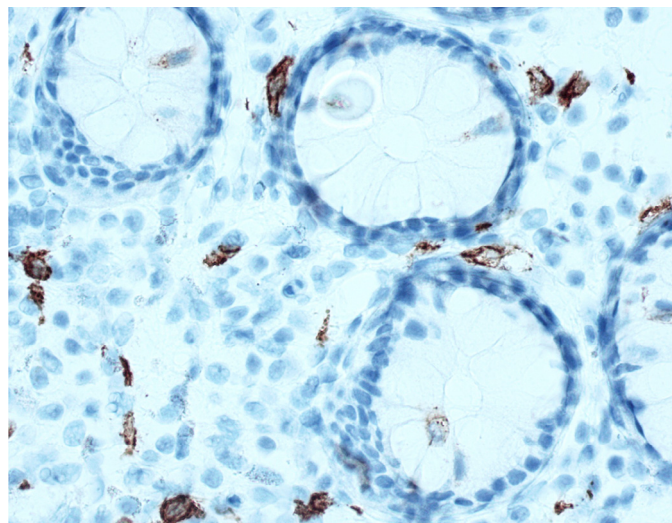


Figure 1. Histological findings of the colonic biopsy specimens. Immunohistochemical staining with CD 117 (c-KIT), using the polyclonal rabbit anti-human CD117 antibody (c-KIT; Dako France, Les Ulis, France) at a 1:400 dilution showed a diffuse infiltration of mast cells (up to 15 mast cells in aggregate) in the lamina propria (original magnification $\times 40$).

during a grade III² NMBA allergy in the general population. Cardiovascular symptoms resolved within a few minutes, whereas a relatively high dose of intravenous epinephrine (cumulative dose up to 500 µg) was required to manage ongoing vasoplegia. However, the additive vasoplegic effect of mastocytosis on the cardiovascular disturbances of IgE-mediated NMBA allergy might have been involved. The relatively high dose of epinephrine also might have been required to compensate for the low-volume resuscitation performed with crystalloids only (500 mL). Accordingly, colloids may be more effective to restore volume loss by vasodilatation and extravasation because of IgE-mediated drug-induced anaphylaxis.^{2,9}

Finally, tryptase rise is usually closely related to the severity of cardiovascular disturbances during IgE-mediated drug allergy.¹⁰ However, tryptase levels measured after the clinical event were inappropriately high compared with a grade III reaction occurring in a general population. This might be partly related to the increased mast cell numbers in mastocytosis as well as the increased releasability of mast cells in clonal mast cell disorders.⁵

In conclusion, this case of NMBA allergy was not linked to SM itself. The clinical phenotype and the management of this case did not differ from NMBA allergy occurring in a healthy population. However, the role of underlying mastocytosis in the clinical presentation cannot be ruled out. Perioperative immediate hypersensitivity needs to be investigated to provide appropriate advice for subsequent anesthetics. In addition, one should remember to investigate for mastocytosis, if relevant.

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Xolair-induced recurrent anaphylaxis through sensitization to the excipient polysorbate



Omalizumab is an anti-immunoglobulin E (anti-IgE) humanized IgG1 monoclonal antibody, indicated for the treatment of moderate-to-severe allergic and uncontrolled asthma. Anaphylaxis was found to occur in 0.1%–0.2% of patients taking Xolair (Novartis, Basel, Switzerland), the commercialized form of omalizumab,¹ with no known underlying mechanism. Although it has been very difficult to develop a reliable assay to detect clinically significant anti-omalizumab IgE, a recent report suggested that Xolair-induced anaphylaxis is not mediated by IgE sensitization to the monoclonal antibody (MAb) omalizumab itself.²

We report the case of a teenager who presented with an anaphylaxis to the first injection of Xolair with positive skin-prick tests to both Xolair and its excipient polysorbate, and cross-reactivity with polyethylene-glycol (PEG)/macrogol.

In 2010, a 15-year-old girl began therapy with Xolair (600 mg every 2 weeks) for severe allergic and uncontrolled asthma. Her IgE level was 4,500 kU/L and her weight was 48 kg. Ten minutes after the first injection, she presented with dyspnea and wheezing requiring inhaled bronchodilator and oral corticosteroids, but

adrenaline was not necessary. The same reaction was noted immediately after the second injection. The third one, performed 30 minutes after antihistamines and inhaled bronchodilator, was well-tolerated. Further injections were given after premedication comprising corticosteroids started 4 days earlier, antihistamines, and inhaled bronchodilator given 30 minutes before the injection. The patient reported better asthma control and less pronounced symptoms after each injection. Xolair was stopped after 5 months because of its decreased efficacy as well as persistent side effects, including dyspnea after each injection, tiredness, headache, and food-induced urticaria.

Three years later, she was referred to our ward for allergological testing of Xolair before its readministration. In fact, she presented several severe asthma crises with one admission to a critical care unit.

The skin-prick test (SPT) to Xolair (150 mg/mL of omalizumab) was positive twice (Table 1) for the patient, yet negative for 5 healthy control subjects who gave their informed consent.

To understand the nature of the molecule responsible for positive SPT to Xolair (the IgG1 MAb omalizumab or an excipient), we set up a series of allergological investigations with SPT to polysorbate 20, the main excipient of omalizumab infusion (other excipients are L-arginine hydrochloride, L-histidine hydrochloride, L-histidine,