

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,

Table 1
Results of Skin Prick Tests

Drug			Skin prick tests				
Brand name	Molecule	Main excipient	Dilution	Polysorbate/PEG concentration present	Wheal (diameter, mm)	Erythema (diameter, mm)	(Wheal + erythema) / 2 (mm)
	Histamine Saline				10 0	45 0	27.5 0
Xolair 1	Omalizumab	Polysorbate 20	150 mg/mL	NA	8	43	25.5
Xolair 2	Omalizumab	Polysorbate 20	150 mg/mL	NA	10	37	23.5
	Polysorbate 20		Pure (1.1 g/mL)	1.1 g/mL	10	32	21
Mabthera	Rituximab	Polysorbate 80	0.1 mg/mL	NA	9	34	21.5
Mabthera	Rituximab	Polysorbate 80	1 mg/mL	NA	7	28	17.5
Remicade	Infliximab	Polysorbate 80	0.4 mg/mL	NA	9	28	18.5
Roactemra	Tocilizumab	Polysorbate 80	0.8 mg/mL	NA	7	34	20.5
Cimzia	Certolizumab pegol	Coupled with polyethylene-glycol (NA)	200 mg/mL	NA	8	22	15
Humira	Adalimumab	Polysorbate 80	50 mg/mL	NA	8	27	17.5
Simponi	Golimumab	Polysorbate 80 + sorbitol	100 mg/mL	NA	10	48	29
	Amoxicillin	Benzyl alcohol	50 mg/mL		0	0	0
Colopeg	Macrogol 3350		Pure	59 g / 69 g	9	33	21
Forlax	Macrogol 4000		Pure	10 g / 10.4 g	8	38	23

NOTE. NA = not available (we were unable to obtain from the pharmaceutical companies the polysorbate/PEG concentrations in the different biotherapies).

and water), and to other MABs either fully human (adalimumab, golimumab), humanized (tocilizumab, certolizumab), or chimeric (rituximab, infliximab). It was not possible to test the omalizumab IgG1 alone, without its excipients. Skin-prick test to polysorbate 20 (pure: 1.1 g/mL) was positive for the patient, yet negative for 7 (4 atopic and 3 non-atopic) controls. Skin-prick tests to all the antibodies tested were also positive (Table 1). We also tested an antibiotic received recently: SPT was negative for amoxicillin. Concerning aeroallergens, most were positive. There was no argument for a mastocytosis, because of a normal serum tryptase level (3 µg/L).

The sensitization to polysorbate explains the positivity of SPT to all biotherapies tested because it is the only excipient present in all those biotherapies, except certolizumab. In its commercialized form, Cimzia (UCB Pharma SA, Colombes, France), certolizumab is coupled with PEG, also called macrogol, a chemical previously reported to cross-react with polysorbate.³ To confirm that positive prick test to Cimzia was related to reactivity to PEG, we realized a last series of SPT with Colopeg (macrogol 3350) and Forlax (macrogol 4000), which were positive with approximatively the same size of wheal and erythema as Xolair and polysorbate 20 (Table 1). Our data are in line with the results of a previous study analyzing the mechanisms of Xolair-induced anaphylaxis in 2 asthmatic patients,⁴ which showed that, despite the fact that none of the patients were IgE- or IgG-sensitized to omalizumab, 1 developed a positive intradermal test to polysorbate.

Although Xolair-induced anaphylaxis is not exceptional,^{1,5} very few studies have analyzed their immune mechanisms.⁶ Here, the patient developed several anaphylactic reactions to Xolair, with positive SPT to Xolair and to polysorbate 20, one of its excipients. Therefore, we concluded that the patient developed a sensitization to polysorbate, which was responsible for the Xolair-induced anaphylaxis. We further showed that this patient had positive SPT to 6 other antibodies (including fully human, humanized, and chimeric antibodies) containing polysorbate or the cross-reactive PEG.

We were surprised to observe that the anaphylactic reactions that developed after each of the 13 subcutaneous injections of Xolair during 5 months were relatively benign. This may be explained by the well-known “anti-allergic” properties of omalizumab, which allow the administration of specific immunotherapy in patients with severe food, insect venom, or drug allergies.⁷ In our case, omalizumab may interact with polysorbate specific IgEs and compete for IgE-mediated mast cell degranulation. This may also be explained by

the anti-allergic premedication with corticosteroids, antihistamines, and aerosols of β₂-adrenergic agonists.

Polysorbates are used in pharmaceutical applications to stabilize emulsions. They are oily liquids derived from PEGylated sorbitan esterified with fatty acids. There are 4 types: polysorbate 20, 40, 60, and 80, with each number assigned to the type of fatty acid associated with the polyoxyethylene-sorbitan. The most commonly used are polysorbate 20 (also named Tween 20) and polysorbate 80. Polyethylene-glycol is the basis of some laxatives and is used as an excipient.

The cross-reactivity of polysorbates and PEG is supported by the literature. Hypersensitivity reactions to polysorbate⁸ and PEG have been reported and cross-reactivity between them has already been described^{3,9} with regard to clinical manifestations and positive SPT. This would be the consequence of a common structure between these 2 polymers—(CH₂CH₂O)_n-. However, the pathophysiology of polysorbate/PEG-induced anaphylaxis is still not well understood. In mice, polysorbate 80 can cause dose-dependent vascular hyperpermeability,¹⁰ which suggests a non-allergic mechanism, probably secondary to mast cell or basophil degranulation. Activation of the complement pathway also seems to be involved.

In conclusion, polysorbate, but not omalizumab, is responsible for the Xolair-induced anaphylaxis observed in the case described. Hypersensitivity to polysorbate seems to be a rare event, but it may explain part of the anaphylaxis induced by Xolair and other polysorbate/PEG-containing biotherapies. Therefore, we recommend performing skin testing with the drug and its excipients in patients developing biotherapy-induced anaphylaxis.

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Safe and effective intradermal influenza vaccine desensitization for delayed influenza vaccine allergy



We report a case of an 18-year-old Japanese male with delayed hypersensitivity to influenza virus vaccine, who completed 7 years of successful annual vaccine desensitization using intradermal trivalent split-virion influenza vaccine (Fluzone, Intradermal, Sanofi Pasteur, Cambridge, Massachusetts). Informed consent was obtained for this report. At 4 years of age, the patient was hospitalized for evaluation of possible compartment syndrome in Japan for his first reaction to the intramuscular influenza vaccine when large circumferential swelling developed over a period of 24 to 48 hours after vaccination, which was successfully treated with intravenous steroids. Although a previous intramuscular influenza vaccination was tolerated before this episode, subsequent influenza vaccination was deferred. The patient was eating eggs without any problems and followed a regular diet. Three years later, he experienced a severe influenza illness requiring admission to the pediatric intensive care unit with intubation. At 9 years of age, he required emergency evaluation for 2 days of worsening respiratory distress, wheeze, productive cough, and temperatures as high as 103°F, with blood pressure 109/55 mm Hg, heart rate 100/min, oximetry 93% on room air, and respiratory rate 20/min. Physical examination was notable for bilateral tonsillar exudate and increased work of breathing with retractions. Enzyme immunoassay was positive for influenza B antigen, and chest x-ray showed right upper lobe and right perihilar opacities consistent with pneumonia. He was again hospitalized, with oxygen therapy, intravenous fluids, and antibiotics. After discharge, he underwent further pediatric allergy outpatient evaluation, where he was found to have specific immunoglobulin E (IgE) sensitizations to latex (1.97 ku/L), porcine gelatin (0.49 ku/L), and egg white (0.7 ku/L), with a total IgE level of 3,778 ku/L. His influenza skin prick test using full-strength Novartis (East Hanover, New Jersey) latex-and-gelatin-free vaccine was negative, with positive intradermal testing (5-mm wheal and 10-mm flare), using a 1:100 v/v dilution of vaccine. After informed consent, the patient underwent intramuscular influenza vaccine desensitization, initially using a multiple-day approach after serial intradermal skin testing to determine a non-reactive starting concentration (Table 1). The patient tolerated the

procedure well, with some mild local soreness and local swelling. The following year, a multiple-day approach using an intradermal vaccine was chosen, which was subsequently transitioned to a single-day protocol. With subsequent delayed full-strength large local reactions up to 120 mm at 24 hours after vaccination (60-mm immediate induration) in 2012, additional dilutions were added to the protocol along with pre- and post-desensitization loratadine 10 mg every morning, cetirizine 10 mg every evening, and as needed topical betamethasone dipropionate to help control his occasional large local reactions. This approach seemed to offer some benefit (for example, maximum of 10 mm immediate induration at full-strength dose recorded in 2017 without concern for delayed reactions). In addition to annual vaccine desensitization, the patient has used oseltamivir prophylaxis with suspected exposures to influenza and has not since required any intensive treatment or hospitalization for subsequent influenza-like illnesses.

Influenza vaccine serves a critical role in reducing influenza virus-associated morbidity and mortality. The Centers for Disease Control and Prevention reports that 80% to 85% of the US influenza-associated pediatric deaths reported in the 2016 to 2017 season occurred in unvaccinated patients.¹ Vaccine hypersensitivity can present a barrier to vaccination; however, vaccine skin testing, graded challenge, and desensitization can allow greater clarity in diagnosis and create avenues to successfully vaccinate allergic populations. In recent years, our understanding of influenza vaccine allergy has evolved, and most influenza vaccine hypersensitivity is known not to be caused by egg allergy but by specific IgE-directed responses to vaccine antigens or excipients such as gelatin.² A recent report of 19 Japanese patients with influenza vaccine allergy described elevated specific IgE to influenza vaccine antigens, whole vaccine products from different manufacturers, and hemagglutinin proteins (A, H1, H3, and B) derived from egg and cell culture when compared with 25 age-matched control subjects. No patient with influenza vaccine allergy in this report had a severe egg allergy.³ Although egg allergy is not an indication for influenza vaccine desensitization or dose challenge,⁴ allergy to another influenza antigen vaccine component is one of the few indications for graded challenge or multi-step desensitization, as was performed in our non-egg-allergic patient.

Influenza vaccine hypersensitivity may be a challenging problem, especially to those allergic to the viral antigen. Not only are these