

Hypersensitivity to COVID-19 Vaccine Confirmed by a Positive Skin Test Result: A Case Report

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We present the case of a 30-year-old woman who experienced an immediate reaction after the first dose of the Pfizer SARS-COV2 vaccine. The reaction was confirmed by skin prick test (SPT).

The patient had a previous history of childhood hepatitis B virus infection treated with interferon and spontaneous chronic urticaria (onset in 2019), which was well controlled with antihistamine treatment (levocetirizine 5 mg every 6 hours). She had never experienced reactions with other drugs.

On January 14 (2021), she received the first dose of the Pfizer SARS-COV2 vaccine. After 5 minutes, she developed pruritic edematous lesions on the trunk, dyspnea, and dizziness. She received one dose of 0.3 mL of epinephrine 1/1000, with complete remission after 30 minutes. Eighteen hours later, she developed extensive edema in the injected arm (from shoulder to hand). She was treated in the emergency room with methylprednisolone and dexchlorpheniramine, and her condition resolved completely in 2 hours.

One week later, in our Allergy Unit, we performed SPTs with polyethylene glycol (PEG, also called Macrogol) 1500 g/mol (0.5 g/ml); PEG 3350 (0.5 g/ml); PEG 4000 (0.5 g/ml); polysorbate 80 (1 g/ml), and polysorbate 20 (pure). The result for polysorbate 80 was positive after 45 minutes (wheal 5 mm, Figure 1), while those for every other excipient remained negative (1 mm). We performed SPT with the Pfizer SARS-COV2 vaccine, which

was positive after 45 minutes (wheal 15 mm, erythema 20 mm, Supplementary Figure 1). Negative and positive control tests were also performed, respectively, with saline (wheal, 1 mm) and histamine (wheal, 10 mm). Intradermal tests with PEGs were not performed in this patient, given the systemic reaction she suffered with the Pfizer vaccine. SPT controls with polysorbate 80 performed on 3 healthy patients were all negative, and SPT controls with the Pfizer SARS-COV2 vaccine were negative in 5 healthy volunteers. We also requested a baseline tryptase, which showed normal values: 4.4 ng/ml.

The Pfizer COVID-19 vaccine contains nucleoside-modified messenger RNA (which encodes the viral spike glycoprotein of SARSCoV-2) [1], and a variant of PEG 2000 g/mol as an inactive ingredient: 2[(polyethylene glycol)-2000]-N, N-ditetradecylacetamide. Polysorbates are derivatives of polyethylene glycol (Polyethylene glycol sorbitans), and they share two chemical moieties, $-(OCH_2CH_2)-$ and $-OCH_2CH_2OH$. Although only sporadically reported, there is evidence for potential cross-reactivity between these polysorbates (Tweens) and PEG [2,3]. We hypothesize that the patient reacted to the Pfizer SARS-COV2 vaccine owing to cross-reactivity between polysorbate 80 (positive skin test result) and PEG 2000 (which is contained in the vaccine), although SPT with PEG were all negative. Increasing the reliability of our observation, a similar case has previously been described by Stone et al [4]: a 51-year-old man who developed anaphylaxis after methylprednisolone acetate injection (contains PEG 3350), and a previous reaction with flushing and hypotension after the use of a PEG 3350 colonoscopy preparation. Skin tests with PEG 3350-containing products were all negative, although the patient tested positive to triamcinolone acetate (which contains polysorbate 80). After challenge with PEG 3350, he developed diffuse urticaria, respiratory distress, and hypotension.

Positive SPT results to polysorbate 80 and Pfizer SARS-COV2 vaccine after 45 minutes are unexpected findings, and although there are no previous references with these products in the literature, Sellaturay et al [5] reported one case of anaphylaxis after medroxy-progesterone acetate with positive SPT to PEG 3350 after 30 minutes. Therefore, they recommend skin prick testing with PEG using a stepwise approach, and

waiting at least 30 minutes before progressing to the next step. To our knowledge, this is the first reported case of hypersensitivity to COVID-19 vaccine confirmed by a positive skin test result, probably due to cross-reactivity owing to the shared chemical moieties in both polysorbate 80 and PEG. Given the presence of polysorbate 80 in many products (such as shampoos and sunscreens) [6] and treatments (such as interferon alfa-2b) [7], the patient may have become sensitized as a consequence of previous exposure to these products. She was under levocetirizine treatment for chronic urticaria (which contains Macrogol (PEG) 400). Some cases of hypersensitivity to Macrogol of high molecular weight (HMW) with tolerance to PEG of low molecular weight (LMW) have been previously described. Wenande et al.[8] described a patient with SPT-confirmed hypersensitivity to PEG 3350 and 6000 with tolerance of oral challenge to an antihistamine with PEG 400 only in the tablet coating. Some authors have hypothesized that HMW PEGs could require lower concentrations to produce hypersensitivity reactions compared to LMW PEGs [2]. The patient has never received the flu vaccine, Hepatitis A nor HPV vaccines, and she had never experienced reactions with other drugs.

Other currently approved COVID-19 vaccines containing polysorbate 80 are: Anhui Zhifei Longcom (RBD-Dimer), Cansino (Ad5-nCoV), Gamaleya (Sputnik V), Janssen (Ad26.COVS.2.S), Vaxzevria (aka Oxford/AstraZeneca) (AZD1222) and Serum Institute of India (Covishield). In phase III are: Novavax (NVX-CoV2373), Clover (SCB-2019), Sanofi/GSK (Recombinant Protein)[9], Medicago (Plant-based VLP) and ReiThera (GRAd-COV2). As for vaccines containing PEG, Moderna mRNA-1273 contains another variant of PEG 2000: 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 [DMG-PEG 2000]), and Curevac (CVnCoV) is currently in phase III. For this reason, and with the aim to provide complete immunization to SARS-CoV-2, we proposed an Allergy study with one of the other available vaccines to the patient, which she rejected.

It is necessary to understand patterns of cross-reactivity between inactive ingredients in COVID-19 vaccines to provide safe options for patients allergic to polysorbates and/or PEG.

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Conflict of interest

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Figure 1. SPT with polyethylene glycol (PEG, also called macrogol) 1500 g/mol (1), macrogol 3350 (2), macrogol 4000 (3), polysorbate 80 (4), and polysorbate 20 (5).



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