## 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-CoV-2 vaccine. After 5 minutes, she developed pruritic edematous lesions on the trunk, dyspnea, and dizziness. She received 1 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 the following: polyethylene glycol (PEG, also known as 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), while those for every other excipient remained negative (1 mm). We performed SPT with the Pfizer SARS-CoV-2 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, given the systemic reaction experienced with the Pfizer vaccine. Control SPTs with polysorbate 80 performed on 3 healthy patients were all negative, and control SPTs with the Pfizer SARS-CoV-2 vaccine were negative in 5 healthy volunteers. We also requested a baseline tryptase determination, 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 SARS-CoV-2) [1] and a variant of PEG 2000 g/mol—2[(polyethylene glycol)-2000]-N,


**Figure.** Skin prick test with polyethylene glycol 1500 g/mol (1), macrogol 3350 (2), macrogol 4000 (3), polysorbate 80 (4), and polysorbate 20 (5).

N-ditetradecylacetamide—as an inactive ingredient. Polysorbates are derivatives of polyethylene glycol (polyethylene glycol sorbitans) and that they share 2 chemical moieties, namely, $OCH_2CH_2$ and $OCH_2CH_2OH$. While only sporadically reported, cross-reactivity between these polysorbates (Tweens) and PEG has been suggested [2,3]. We hypothesize that the patient reacted to the Pfizer SARS-CoV-2 vaccine owing to cross-reactivity between polysorbate 80 (positive skin test result) and PEG 2000 (which is contained in the vaccine), although the results of SPTs with PEG were all negative. The reliability of our observation is enhanced by the report of a similar case by Stone et al [4], where a 51-year-old man developed anaphylaxis after a methylprednisolone acetate injection (contains PEG 3350) and a previous reaction with flushing and hypotension after administration of a PEG 3350 colonoscopy preparation. Skin tests with PEG 3350–containing products were all negative, although the patient tested positive with 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-CoV-2 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 a case of anaphylaxis after medroxy-progesterone acetate with a positive SPT result to PEG 3350 after 30 minutes. Therefore, these authors recommended SPT with PEG using a stepwise approach and

 

waiting at least 30 minutes before progressing to the following step. To our knowledge, this is the first reported case of hypersensitivity to COVID-19 vaccine confirmed by a positive SPT result, probably owing to cross-reactivity of the shared chemical moieties in both polysorbate 80 and PEG. Given the presence of polysorbate 80 in many products (eg, shampoos and sunscreens) [6] and treatments (eg, interferon alfa-2b) [7], the patient may have become sensitized because of previous exposure to these products. She was receiving levocetirizine (which contains macrogol [PEG] 400) for chronic urticaria. Hypersensitivity to high-molecular-weight (HMW) macrogol with tolerance to low-molecular-weight (LMW) PEG has been described. Wenande et al [8] reported the case of a patient with SPT-confirmed hypersensitivity to PEG 3350 and 6000 who tolerated an 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 than LMW PEGs [2]. The patient has never received the influenza, hepatitis A, or human papillomavirus vaccines and has never experienced reactions with other drugs.

Other currently approved COVID-19 vaccines containing polysorbate 80 include the following: Anhui Zhifei Longcom (RBD-Dimer), Cansino (Ad5-nCoV), Gamaleya (Sputnik V), Janssen (Ad26.COV2.S), Vaxzevria (aka Oxford/AstraZeneca) (AZD1222), and Serum Institute of India (Covishield). Preparations currently in phase 3 include 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, namely, 1.2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (DMG-PEG 2000]), and Curevac (CVnCoV) is currently in phase 3. For this reason, and with the aim of providing complete immunization to SAR-CoV-2, we proposed an allergy study with one of the other available vaccines, which the patient rejected.

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

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*Conflicts of Interest*

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