## COVID-19 Vaccine Tolerability in a Patient With a Delayed Allergic Reaction to Polyethylene Glycol: A Case Report

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Since the beginning of the COVID-19 vaccination campaign in December 2020, multiple cases of suspected allergic reactions have been reported, with an initial estimation of 11.1 reactions (including anaphylaxis) per 1 million doses [1,2]. The excipient polyethylene glycol 2000 (PEG-2000) has been considered the potential cause of immediate drug hypersensitivity reactions to the COVID-19 vaccines that contain it, namely, Spikevax (Moderna) and Cominarty (Pfizer-BioNTech) [3,4]. PEG is a polyether compound that is widely used as an additive in pharmaceuticals, food, and cosmetics owing to its stabilizing properties [5]. For medicines, the process of PEGylation involves binding of PEGs to systemic drugs to increase molecular weight, prolong circulation time, and shield the drug from the immune system by preventing opsonization [6]. In these vaccines, PEG-2000 is used to encapsulate messenger RNA (mRNA) into lipid nanoparticles and thus deliver it to cells [5]. Expert consensus statements have provided guidelines on the diagnostic and therapeutic procedures used in COVID-19 vaccination in patients with allergic diseases and for patients who experienced an immediate reaction to a COVID-19 vaccine [2], although there is no information concerning COVID-19 vaccination in patients with PEG-allergic contact dermatitis. We present the case of a patient diagnosed with contact dermatitis due to PEG who received a COVID-19 vaccine containing PEG-2000 without complications. The patient gave her consent for publication of her case.

A 41-year-old woman with no medical history of interest or drug allergy background was seen at the dermatology department because of symptoms of stomatitis that she suspected were related to toothpaste, mouthwash, and chewing gum. An allergy study was performed using patch tests with the patient's products (Oral-B toothpaste and mouthwash), the Spanish standard patch test series [7], and the cosmetics/vehicles and emulsifier series (Supplementary Table 1). The results were mild positive at 96 hours to PEG-400 and Oral-B toothpaste and mouthwash (which contain PEG-300, also named PEG-6 according to the International Nomenclature of Cosmetic Ingredients); therefore, she was diagnosed with allergic contact stomatitis to PEG. Avoidance of PEG-containing products (toothpaste and mouthwash) was recommended, and the oral symptoms resolved.

Some months later, the patient was referred to our allergy department to assess the possibility of receiving the third dose of COVID-19 vaccination with PEG-containing vaccines, which, at that time, were the only ones available in our hospital. Previously, she had received 2 doses of Vaxzevria (AstraZeneca), which does not contain PEG. We performed an allergy work-up based on skin prick tests with PEG-1500 (100 mg/mL, ROXALL Medicina España S.A.) and a 1:100 dilution of polysorbate 80 (4 mg/mL) and intradermal testing with 1:100 and 1:1000 dilutions of PEG-1500 (1 mg/mL, ROXALL Medicina España S.A.) and a 1:100 dilution of polysorbate 80 (4 mg/mL). The results were negative in the immediate and late readings. The allergology work-up could not be performed with PEG-2000, since it is not commercially available.

Given these results and taking into account the risk of insufficient immunization, the patient decided to receive a third dose of COVID-19 vaccine. She received Spikevax (a PEG-2000–containing vaccine) at our hospital's vaccination center, and no immediate or delayed adverse reactions were reported.

In the present case, the stomatitis symptoms and positive patch test results confirmed a delayed type IV hypersensitivity reaction to PEG. Some studies have reported that low-molecular-weight (LMW) PEGs (eg, 200-400 g/mol) are implicated mainly in allergic contact dermatitis, and cross-reactivity has been reported between LMW PEGs (<400 g/mol) but not with high-molecular-weight (HMW) PEGs (>1000 g/mol) [3,4]. In the case we report, the toothpaste and mouthwash contained PEG-300, an LMW PEG, thus accounting for the tolerability of PEG-2000 (an HMW PEG) in the COVID-19 vaccines.

Similar scenarios were reported with other drug excipients, such as thimerosal. Thimerosal is a contact allergen composed of a mercury derivative and a thiosalicylic acid and is used in cosmetics, vaccines, and eye care products [8]. Despite the apparent sensitization to mercurial drugs, probably induced by vaccination, some clinical studies demonstrated that further vaccination of affected individuals with thimerosal-containing vaccines was safe, with no hypersensitivity reactions reported, even in persons with a positive patch test result to thimerosal, suggesting that hypersensitivity to thimerosal was not associated with an increased risk of vaccination reactions [8-10].

In conclusion, although we may see patients diagnosed with contact dermatitis caused by sensitization to PEG, we should not rule out the possibility of offering patients safe vaccination, even with PEG-2000–containing COVID-19 vaccines. Future studies will be needed to help us clarify the true role of hypersensitivity to PEG and the risk of administering PEG-containing vaccines, especially given that the benefits of vaccination clearly outweigh the small risk of local dermatitis.

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*Conflicts of Interest*

The authors declare that they have no conflicts of interest.

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