Polyethylene Glycol Allergy and Immediate-Type Hypersensitivity Reaction to COVID-19 Vaccination: Case Report

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In December 2020, the Pfizer-BioNTech and Moderna coronavirus disease 2019 (COVID-19) vaccines were approved and implemented in the battle against infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). These vaccines are now widely used, and cases of anaphylaxis after administration have been reported. In the US, anaphylaxis affects 4.7 and 2.5 patients per million doses administered for the Pfizer-BioNTech and Moderna vaccines, respectively [1]. In comparison, the average for vaccine-associated anaphylaxis has been estimated at 1 case per million injections. A common cause has not yet been identified, and excipients seem to be a more likely culprit than the active ingredient [2]. The polyethylene glycol (PEG)–modified lipids used as excipients in the Pfizer-BioNTech and Moderna mRNA vaccines contain 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide and polyethylene glycol (PEG) 2000 dimyristoyl glycerol, respectively. Polysorbate 80 has been suggested as a potential allergen in the pneumococcal conjugate vaccine and other drugs, and cross-reactivity between PEG and polysorbate, although rare, has been reported [3,4]. Hence, patients with a pre-existing immediate-type allergy to PEG, polysorbate, or other vaccine excipients are prohibited from receiving Pfizer-BioNTech and Moderna mRNA. However, to date, data demonstrating that an excipient could be a cause of COVID-19 vaccine–induced anaphylaxis are limited [5-7].

We present the case of a 50-year-old health care worker with a history of nonsteroidal anti-inflammatory drug (NSAID)–induced angioedema who developed an immediate-type hypersensitivity reaction after administration of the COVID-19 Comirnaty vaccine (Pfizer-BioNTech). Ten minutes after receiving the vaccine, the patient began to feel unwell and light-headed. Her blood pressure was normal (measured, but not recorded), and she felt reassured. Thirty minutes after vaccination, she developed generalized urticaria, pruritus, and lip angioedema. She was re-examined by a physician, who administered 2 oral doses of desloratadine 5 mg, and her symptoms improved. No late responses were noted, although she continued to feel unwell up to 24 hours after receiving the vaccine. No NSAIDs were taken prior to the vaccination.

She was advised not to receive her second dose, and an allergy work-up was performed 5 weeks after the event. Baseline tryptase was normal (5.7 µg/L, normal <11.0 µg/L); tryptase after the reaction was not determined despite national recommendations. Specific IgE (ImmunoCAP, Phadia) to chlorhexidine, latex, and ethylene oxide was negative (<0.01 aU/mL). Skin prick tests (SPTs) were undertaken sequentially to PEG 400 (undiluted), 4000 (100 mg/mL), and polysorbate 80 (1 mg/mL). Intradermal testing (IDT) with polysorbate 80 was also performed. However, after SPT with PEG 4000 (0.1 mg/mL), the patient developed pruritus on her arm, with no positive skin test result or visible skin lesions. Fifteen minutes after SPT with PEG 4000 (1 mg/mL), she developed a generalized urticarial rash on both arms and the trunk (Figure S1). No wheals were noted at any of the SPT sites. The patient was given 2 sublingual doses of ebastine 20 mg, and her symptoms resolved. She considered the reaction to be reminiscent of that which occurred after the COVID-19 vaccination. Sellaturay et al [8] reported a case with urticaria and hypotension 30 minutes after IDT with PEG, although SPT and IDT results remained negative, as in the case we report. Serum tryptase measured immediately after onset of symptoms remained unchanged. A week later, SPT and IDT with polysorbate 80 were repeated and yielded negative results, as did SPT for methylprednisolone acetate (containing 29 mg/mL PEG 3350 according to the manufacturer). No IDT was performed to avoid potentially severe reactions to IDT with PEG, and the patient was discharged [8]. However, she later reported that while returning home she experienced tingling and angioedema of the tongue and diffuse itching with urticaria on both arms. These symptoms resolved with oral antihistamine. Two weeks later, SPT was undertaken with PEG 400 (1/100) and the COVID-19 Comirnaty vaccine (1/100, 1/10); the results were positive to both (Figure S1). A basophil activation test (BAT) for PEG 4000, polysorbate 80, and the COVID-19 Comirnaty vaccine was negative. As indicated elsewhere, the sensitivity of the BAT in PEG allergy is considered limited. An overview of the tests performed is provided in Table S1. Advances in PEG skin testing have been described, suggesting a stepwise buildup of each concentration of PEG, as well as of the molecular weight of the PEG tested [4-9].

The patient was diagnosed with a possible COVID-19 vaccine–induced immediate-type hypersensitivity due to a hitherto unidentified PEG allergy. Given the negative skin test results for polysorbate 80, the patient received the Janssen COVID-19 vaccine, which contains polysorbate 80 and not PEG as an excipient. No subsequent hypersensitivity reaction was observed. Allergy to PEG is typically characterized by reactivity for PEG from a certain molecular weight or higher, with reactivity to at least PEG 400-4000, as in the present case [8]. From a diagnostic viewpoint, other causes must also be considered. Cases of urticaria and angioedema after COVID-19 vaccination have been reported, especially in the context of chronic spontaneous urticaria, which was not reported in the present case.

As suggested by Caballero et al [10], a thorough clinical history of previous exposures and reactions to the excipients

administered should be obtained, as with bowel preparations. In this case, there were no previous reactions to PEG-containing products. The patient experienced angioedema after exposure to multiple NSAIDs, some of which contained PEG, suggesting that angioedema was induced by NSAIDs and not by PEG. It should also be noted that some brands of oral antihistamines contain PEG. In the present case, desloratadine given to the patient by the general practitioner contained macrogol 400 in the tablet coating, whilst ebastine in our center did not. Antihistamines without PEG should be available when testing for potential PEG/polysorbate allergy. Patients experiencing anaphylaxis upon COVID-19 vaccination require a further allergy work-up, including evaluation for PEG and polysorbate 80 allergy via skin testing. However, a threshold for testing has not been established, and, in the present case, the patient only experienced mild symptoms. Furthermore, no data on systematic evaluation of patients experiencing anaphylaxis have been reported. We also recommend evaluation to investigate underlying clonal mast cell disorder (baseline tryptase), chlorhexidine (a commonly used disinfectant that could be a hidden culprit), latex (not present in the vaccine, but a reaction could be caused through contact with a health care worker), and ethylene oxide (for instance, used to sterilize tuberculin syringes, which are often used for administration of vaccines). Prior COVID-19 infection and baseline serology could serve as potential markers of pre-existing immunity to SARS-CoV-2.

In conclusion, we report a case of COVID-19 vaccine–induced immediate-type hypersensitivity reaction in which allergy to PEG was identified as the culprit. The reaction itself was easily and well managed. We believe that an allergy work-up could be useful in these rare cases.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Shimabukuro TT, Cole M, Su JR. Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US-December 14, 2020-January 18, 2021. JAMA. 2021;325:1101-2.
2. Castells MC, Phillips EJ. Maintaining Safety with SARS-CoV-2 Vaccines. N Engl J Med. 2021;384:643-9.
3. Stone CA Jr, Liu Y, Relling MV, Krantz MS, Pratt AL, Abreo A, et al. Immediate Hypersensitivity to Polyethylene Glycols and Polysorbates: More Common Than We Have Recognized. J Allergy Clin Immunol Pract. 2019;7:1533-40.
4. Wenande E, Garvey LH. Immediate-type hypersensitivity to polyethylene glycols: a review. Clin Exp Allergy. 2016;46:907-22.
5. Banerji A, Wickner PG, Saff R, Stone CA Jr, Robinson LB, Long AA, et al. mRNA Vaccines to Prevent COVID-19 Disease and Reported Allergic Reactions: Current Evidence and Suggested Approach. J Allergy Clin Immunol Pract. 2021;9:1423-37.
6. Sellaturay P, Nasser S, Islam S, Gurugama P, Ewan PW. Polyethylene glycol (PEG) is a cause of anaphylaxis to the Pfizer/BioNTech mRNA COVID-19 vaccine. Clin Exp Allergy. 2021;51:861-3.
7. Wolfson AR, Robinson LB, Li L, McMahon AE, Cogan AS, Fu X, et al. First Dose mRNA COVID-19 Vaccine Allergic Reactions: Limited Role for Excipient Skin Testing. J Allergy Clin Immunol Pract. 2021;J21:675-9.
8. Sellaturay P, Nasser S, Ewan P. Polyethylene Glycol-Induced Systemic Allergic Reactions (Anaphylaxis). J Allergy Clin Immunol Pract. 2021;9:670-5.
9. Bruusgaard-Mouritsen MA, Jensen BM, Poulsen LK, Johansen JD, Garvey LH. Optimizing investigation of suspected allergy to polyethylene glycols. J Allergy Clin Immunol. 2022;149(1):168-75.e4.
10. Caballero ML, Quirce S. Excipients as Potential Agents of Anaphylaxis in Vaccines: Analyzing the Formulations of Currently Authorized COVID-19 Vaccines. J Investig Allergol Clin Immunol. 2021;31:92-3.

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