Polyethylene glycol allergy and immediate-type hypersensivitity reaction to COVID-19 vaccination: case report

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As of December 2020, the Pfizer-BioNTech and Moderna coronavirus disease 2019 (COVID-19) vaccine have been approved and implemented in the battle against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). These vaccines are now being widely used and cases of anaphylaxis after administration have been reported. The most estimated reporting rates for anaphylaxis in the US for the Pfizer-BioNTech or Moderna vaccination are 4.7 and 2.5 cases/million doses administered, respectively [1]. In comparison, the average vaccine-associated anaphylaxis has been estimated at one case per million injections. A common cause has not been identified and excipients have been suggested as a more likely culprit compared with active agent [2]. Polyethylene glycol (PEG)-modified lipids are used in the Pfizer-BioNTech and Moderna mRNA vaccine, containing 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide and polyethylene glycol [PEG] 2000 dimyristoyl glycerol [DMG] respectively. Polysorbate 80 has been suggested as a potential allergen in amongst others the conjugated pneumococcal vaccine and, rarely, cross-reactivity between PEG and polysorbate has been reported [3, 4]. Hence, patients with a pre-existing immediate-type allergy to PEG, polysorbate or other excipients in vaccines are prohibited to receive these vaccines. However, to date, there are limited data demonstrating that an excipient could be a cause of COVID-19 vaccine-induced anaphylaxis [5-7].

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We present a case of a 50-year-old female health care worker with a history of 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 she began to feel unwell and light-headed. Blood pressure was normal (measured, but not registered) and the patient was reassured. At 30 minutes post-vaccination, she developed generalized urticaria, pruritus and lip angioedema. The patient was re-examined by a physician who administered 2 oral doses of desloratadine 5 mg, with improvement of symptoms. No late responses were noted although the patient 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 workup 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, Sweden) to chlorhexidine, latex, and ethylene oxide were negative (<0.01 aU/mL). Skin prick tests (SPTs) were sequentially undertaken to PEG 400 (undiluted), 4000 (100 mg/mL), and polysorbate 80 (1 mg/mL). Intradermal testing (IDT) with polysorbate 80 was also commenced. However, after SPT with PEG 4000 (0.1 mg/mL) the patient developed pruritus on her arm without skin test positivity or visible skin lesions. Fifteen minutes after SPT with PEG 4000 (1 mg/mL) the patient developed a generalized urticarial rash predominant at both arms and trunk (Figure S1). No wheal was noted at any of the SPT sites. The patient was given 2 sublingual doses of ebastine 20 mg, with resolution of symptoms. For the patient, the reaction was reminiscent to that after the COVID-19 vaccination. Sellaturay et al. reported a case with urticaria and hypotension 30 minutes after IDT with PEG although SPT and IDT itself remained negative, as in our patient [8]. Serum tryptase level measured immediately after onset of symptoms was unchanged. A week later, SPT and IDT with polysorbate 80 was repeated and negative as was SPT for methylprednisolone-acetate (known to contain 29 mg/mL PEG 3350, information obtained from the manufacturer). No IDT was performed to avoid potential severe

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reactions to IDT with PEG and the patient was discharged [8]. However, later she reported that while returning home she experienced tingling and angioedema of the tongue and diffuse itching with urticaria on both arms, responsive to an oral antihistaminicum. Two weeks later, SPT with PEG 400 (1/100) and the COVID-19 Comirnaty® vaccine (1/100, 1/10) were undertaken which were both positive (Figure S1). A basophil activation test (BAT) for both PEG 4000, polysorbate 80 and the COVID-19 Comirnaty® vaccine was negative. As indicated in prior work, sensitivity of BAT in case of PEG allergy is considered limited. An overview of the tests performed is provided in Table S1. Advances on PEG skin testing have been described, suggesting a stepwise buildup of the concentration of each PEG as well as of the molecular weight (MW) of the tested PEG [4-9].

A diagnosis of COVID-19 vaccine-induced immediate-type hypersensitivity due to a hitherto unidentified PEG allergy was made. Given the negative skin tests for polysorbate 80, our patient received the Janssen COVID-19 vaccine, that contains polysorbate 80 and not PEG as an excipient, without a repeat hypersensitivity reaction. Allergy to PEG is typically characterized by reactivity for PEG from a certain molecular weight or higher (MW), with in our case reactivity to at least PEG 400-4000 [8]. From a diagnostic viewpoint other causes need to be considered too. Cases of urticaria and angioedema after COVID-19 vaccination have been described, especially in the context of chronic spontaneous urticaria, absent in our patient.

Second, as suggested by Caballero et al., a thorough clinical history of previous exposures and reactions to the administered excipients, as for example in bowel preparations, should be obtained [10]. In this case, there were no previous noted reactions to PEG-containing products. This patient experienced angioedema after exposure to multiple NSAID, yet some containing PEG and others not, suggesting in our case these were NSAID- and not PEG-driven. Lastly, it should also be noted that some brands of oral antihistamines contain PEG. In our case, desloratadine given to the patient by the general practitioner did contain macrogol 400 in the tablet coating, whilst ebastine in our center did not.

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Antihistamines without PEG should be available when testing for potential PEG/polysorbate allergy. Patients experiencing anaphylaxis upon COVID-19 vaccination require a further allergy workup, including evaluation for PEG and polysorbate 80 allergy via skin testing. However, a threshold when to test, as our cases only experienced mild systemic symptoms, has not been established and results of a systematic evaluation in those experiencing anaphylaxis has not been reported. We also recommend evaluation for an underlying clonal mast cell disorder (baseline tryptase), chlorhexidine (an often used disinfectant that could serve as a hidden culprit), latex (not present in the vaccine, but possible used by the administrating health care worker), and ethylene oxide (for instance used to sterilize tuberculin syringes often used for administration of vaccines). Prior COVID-19 infection and baseline serology could serve as potential markers of pre-existing immunity to SARS-CoV2.

In conclusion, we report a case of a COVID-19 vaccine-induced immediate-type hypersensitivity reaction in whom an allergy to PEG was identified as the culprit. The reaction itself was easily and well-managed. We indicate an allergy workup can be useful in these rare patients.

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Conflict of interest

MH, MV, RS have no conflict of interest related to this work.

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