Received: 1 June 2021 | Accepted: 25 July 2021

DOI: 10.1111/cea.13995

CORRESPONDENCE

WILEY

IgE-mediated allergy to polyethylene glycol (PEG) as a cause of anaphylaxis to mRNA COVID-19 vaccines

To the editor,

Anaphylactic reactions to mRNA COVID-19 vaccines have been reported, with the polyethylene glycol (PEG) they contain being considered a possible culprit allergen.[1] Sellaturay et al describe a patient who had a past anaphylactic reaction to a PEG-containing oral medication and urticarial reactions to topical application of PEG-containing personal care products, who subsequently had an anaphylactic reaction to the Pfizer/BioNTech mRNA COVID-19 vaccine.[2] It is likely that this patient's anaphylactic reaction to the vaccine was the result of IgE-mediated allergy to PEG as the authors conclude. The result of her prick skin test to a 1% (10 mg/ml) solution of PEG 4000 was positive and also induced an anaphylactic reaction. This implies that she is exquisitely sensitive to PEG, since prick skin testing introduces only a tiny amount of the tested substance into the skin. However, the result of a prick skin test with the Pfizer/BioNTech mRNA COVID-19 vaccine itself, which contains 0.05 mg 2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide per 0.3 ml dose (0.17 mg/ml) in the nanoparticles that deliver the mRNA,[3] was negative. The likely explanation for this is that, even in this highly PEG-allergic patient, not enough PEG was introduced into the skin by the prick test with the vaccine to produce a positive result. An intradermal skin test with the vaccine was not performed, presumably due to the risk of a systemic reaction in this patient.

As the authors note, there were some potentially inconsistent features of her case. First, her serum mast cell tryptase level was not elevated with her anaphylactic reaction to the vaccine nor with her anaphylactic reaction to the PEG prick skin test, although this does not exclude the diagnosis. Second, her prick skin test results were positive only to PEG 4000 and not to higher molecular weight PEGs, although as they suggest, this may have been due to a delay in reaction time and suppression by treatment. Anaphylaxis is a clinical diagnosis, and the patient's constellation of symptoms is certainly consistent with this,[4] yet there is a differential diagnosis to include immunization stress-related response.[5,6]

The positive PEG skin test result demonstrates mast cell degranulation, but not the mechanism of this degranulation, which is likely IgE-mediated, but could also include other mechanisms such as direct engagement of other mast cell receptors such as Mas-Related G Protein-Coupled Receptor-X2 (MRGPRX2) or complement activation-related pseudoallergy (CARPA). Another recent publication, using skin testing as well as basophil activation testing (BAT), suggests that PEGylated nanoparticles may be better able than PEG alone to cross-link cell-bound IgE or stimulate CARPA reactions.[7] However, serum-specific IgE assays to PEGylated nanoparticles were not performed and the BAT assay was not performed on patients who had actually had apparent allergic reactions to vaccine administration.[8]

Given the importance of determining definitively that IgE-mediated allergy to the PEG contained in mRNA COVID-19 vaccines can be a cause for anaphylactic reactions to these vaccines, it would seem appropriate to pursue additional evaluation of the patient reported by Sellaturay et al. These tests could include using the patient's serum for specific IgE antibody testing ("RAST"), an inhibition immunoassay ("RAST inhibition") and a gel electrophoresis / immunoblotting assay (analogous to Western blot, but looking for IgE to PEG and other non-protein vaccine constituents), all using PEGs of various molecular weights and the vaccines themselves.

CONFLICT OF INTEREST

None.

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How to cite this article: Kelso JM. IgE-mediated allergy to polyethylene glycol (PEG) as a cause of anaphylaxis to mRNA COVID-19 vaccines. *Clin Exp Allergy*. 2022;52:10–11. https://doi.org/10.1111/cea.13995