Polyethylene Glycol Allergy: Risks of Skin Testing and Complement-Mediated Anaphylaxis

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Many severe immediate-type allergic reactions to COVID-19 vaccines, including anaphylaxis, have been attributed to allergy to excipients, such as polyethylene glycol (PEG), which is found in the Fosun-Pharma Pfizer BioNTech vaccine (BNT). Classically, immediate-type hypersensitivity reactions such as anaphylaxis have been attributed to IgE-mediated reactions. However, complement-mediated reactions, such as complement activation–related pseudoallergy (CARPA), have been postulated with PEG and COVID-19 vaccine–associated allergies. These reactions are triggered by activation of the complement cascade, which produces C3a, C4a, and C5a anaphylatoxins [1]. However, evidence for CARPA following exposure to PEG has been scarce. We describe a case of severe anaphylaxis elicited by skin testing with PEG and the subsequent in vitro work-up supporting a complement-mediated process.

A 48-year-old man was referred to our Vaccine Allergy Safety Clinic for evaluation of suspected PEG allergy prior to COVID-19 vaccination. He had a history of suspected immediate-type hypersensitivity after ingestion of Klean-Prep (Helsinn-Birex Pharmaceutical), which contains PEG 3350. He had no other known drug allergies and there was no history of atopy. Around 9 years ago, he developed generalised urticaria 15 minutes after ingestion of Klean-Prep before elective colonoscopy. His symptoms were self-limiting, and there were no features of systemic involvement.

The patient consented to allergy testing with PEG, as per departmental protocol. Skin testing was performed with PEG 3350 (1/10 concentration). Ten minutes after intradermal testing (IDT), the patient complained of generalised pruritus and chills. No rash or other mucocutaneous manifestations were observed, and IDT to PEG 3350 was unequivocally negative. He then experienced dizziness and severe hypotension (systolic BP of 55 mmHg). He was given 2 doses of intramuscular adrenaline and intravenous fluids without improvement, and intravenous adrenaline was required before his blood pressure returned to normal.

Once the patient's condition had stabilized, investigations showed significantly elevated tryptase of 22.7 ng/mL (baseline level 4.8 ng/mL), thus confirming the diagnosis of anaphylaxis. Soluble C5b-9 complex (Sc5b-9), also known as the terminal complement complex, was determined as per the recommendation of the Centers for Disease Control and Prevention [2] and found to be significantly elevated (257.2 g/mL [reference range, 75-219 ng/mL]), indicating activation of the complement system. IgG against PEG was detected in the patient's serum by enzyme-linked immunoassay (ELISA) with an antibody activity threshold index of 4.0 (positive antibody activity defined as values >1.0).

Six weeks after the event, basophil activation tests (BATs) were performed using the patient's basophils with PEG and the BNT vaccine. Flow cytometry showed significant upregulation of CD63c and CD203c after stimulation with BNT, although basophils remained nonresponsive to stimulation with multiple molecular weights of PEG (PEG 2000, 3350, and 4000) (Figure). The patient was advised to avoid all PEG-containing compounds in the future and received a non–PEG-containing COVID-19 vaccine (CoronaVac, SinoVac) with no reactions.

Immediate-type hypersensitivity reactions such as anaphylaxis are traditionally defined as IgE-mediated reactions. However, non–IgE-mediated mechanisms, such as CARPA, have been postulated in PEG and COVID-19 vaccine allergies [3]. The wide heterogeneity of clinical presentations and laboratory work-up of PEG-associated allergy may be due to the differing proportions of IgE- and complement-mediated mechanisms contributing to the reaction.

To the best of our knowledge, this is the first report of a confirmed case of PEG-induced anaphylaxis (based on clinical criteria and significantly elevated serum tryptase) following skin testing with evidence of CARPA seen as significantly elevated Sc5b-9. Elevated tryptase or a positive BAT result cannot distinguish between IgE-mediated and non–IgE-mediated causes of mast cell degranulation [4.5]. On the other hand, Sc5b-9 is a by-product of the complement cascade activation that is elevated in complement-mediated reactions [6], as exemplified by this case. Anti-PEG IgG antibodies are thought to play a role in pathogenesis and were present in the patient's serum. The anti-PEG IgG ELISA not only detects the presence of antibodies, but also measures anti-PEG activity, which combines the antibody concentration and avidity for the PEG antigen. These antibodies activate the complement cascade upon binding to PEG or PEGylated substances, with formation of immune complexes, leading to activation of the complement cascade via the classical pathway, producing C3a, C4a, and C5a anaphylatoxins, and inducing degranulation of basophils and mast cells [1, 7].

Various conjugations and formulations of PEG are used in the work-up for suspected PEG allergies. The BAT performed in the present case yielded positive results to BNT, but not to purified PEG, even at different molecular weights. This finding has been well documented and is likely due to the increase in immunogenicity when PEG is conjugated with lipid nanoparticles [8,9]. The anti-PEG antibody ELISA also uses PEG conjugated to bovine serum albumin and not

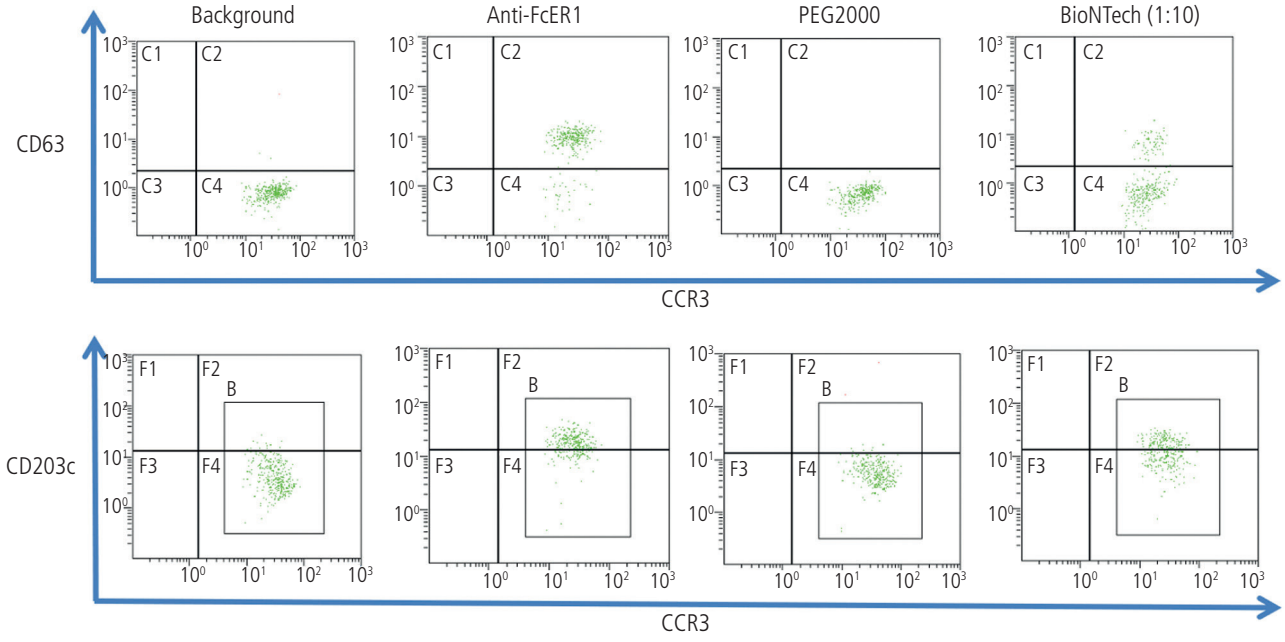

Figure. Basophil activation test results for the BioNTech vaccine and polyethylene glycol.

purified PEG as the target antigen. This may also explain the persistent negative skin testing results recorded throughout the allergic reaction.

The patient was only exposed to PEG twice, once after ingestion of Klean-Prep and once after skin testing with PEG 3350, suggesting that purified PEG undergoes changes in conformation or chemical structure after conjugation with organic substances and is able to induce allergic reactions in vivo. This phenomenon warrants further research and investigation.

We report a case of severe anaphylaxis induced by skin testing with purified PEG. Although elevated tryptase levels and positive BAT results support the diagnosis of an immediate-type hypersensitivity reaction, a comprehensive work-up including Sc5b-9 and positive IgG antibodies against PEG suggests the role of complement-mediated mechanisms. Our report also highlights the importance of choosing conjugated forms of PEG, such as PEG-containing vaccines, for in vitro testing to ensure a more accurate work-up of suspected cases. Furthermore, in vivo allergy investigations may also carry considerable risk. We therefore suggest cautious skin testing by starting with skin prick tests and only considering IDT (at progressive dilutions) if skin prick tests are negative. All investigations should be conducted in a specialist drug allergy center equipped with trained personnel and adequate resuscitation equipment, with venous access ensured as a precaution against severe reactions.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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