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Non–immunoglobulin E-mediated allergy associated with Pfizer-BioNTech coronavirus disease 2019 vaccine excipient polyethylene glycol

The development of safe and efficacious coronavirus disease 2019 (COVID-19) vaccines has been pivotal in nanomedicine research, helping to curtail further spread of the severe acute respiratory syndrome coronavirus 2 virus. Although severe immunologic reactions to the vaccine are rare, fear of allergic reactions impedes global vaccination efforts. Understanding the mechanism of these allergic reactions is important for informing guidelines, including contraindications, to COVID-19 vaccines and for the development of next-generation vaccines with improved safety. We introduce a severe case of a non–immunoglobulin E (IgE)-mediated hypersensitivity resulting in an immediate-type reaction to the Pfizer-BioNTech COVID-19 vaccine.

A 56-year-old woman received her first dose of the Pfizer-BioNTech messenger RNA (mRNA) vaccine (BNT162b2). Approximately 5 minutes after administration, she felt dizzy, lightheaded, dyspneic, throat tightening, and abdominal pain. Initial blood pressure was 145/94 mm Hg; a repeat reading minutes was later done with a blood pressure of 70/42 mm Hg and a pulse rate of 150 beats/minute. Her physical examination was notable for faint end-expiratory wheezes. Her systolic blood pressure further fell to the 50s and a code blue was called for additional resources. Intramuscular epinephrine was administered immediately after code blue team arrival and after 2 minutes, her blood pressure recovered to 176/77 mm Hg. Although her symptoms transiently improved, she continued to have waves of chest tightness and dyspnea requiring 2 subsequent doses of 0.3 mg of intramuscular epinephrine followed by a 20-μg bolus of epinephrine intravenously, and initiation of an epinephrine infusion at 0.1 μg/kg/min. In addition, she received lactated ringer's solution, racemic epinephrine and albuterol nebulizer, famotidine, diphenhydramine, and methylprednisolone (Methylprednisolone, Pfizer, New York, New York), and was admitted to the intensive care unit. In the intensive care unit, her vital signs improved, and she was weaned off of the epinephrine infusion 3 hours later. She did not require supplemental oxygen and her wheezing resolved. Tryptase level was collected approximately 90 minutes after the index event, which was 6 ng/mL (reference range < 11.5 ng/mL). There were no further objective signs of a biphasic or protracted anaphylactic reaction, and she was ultimately discharged from the hospital after 5 days with epinephrine injector pens. The patient was instructed not to receive the second dose of the Pfizer-BioNTech vaccine and was enrolled in the national vaccine adverse event reporting system. Allergy testing was pursued on a follow-up clinic visit after 21 days.

The patient received skin prick testing (SPT) to undiluted BNT162b2 vaccine, polyethylene glycol (PEG) (a small lipophilic excipient in both Pfizer-BioNTech and Moderna vaccines), and polysorbate 80 (a known cross-reactant to PEG). Histamine and normal saline were used as positive and negative controls, respectively.

Whole blood was obtained from the patient, and activation markers, which are up-regulated on basophils during a hypersensitivity reaction, were measured in vitro using flow cytometry. Blood was heparinized, stored in a 4°C cold room on a rocker, and aliquoted and analyzed within the same day. Dilutions of dimyristoyl glycerol-polyethylene glycol (DMG-PEG) 2000 (Avanti Polar Lipids, Alabaster, Alabama) were prepared and then stored at 4°C. Using sterile tubes, 100 μL of heparinized blood was stimulated with 100 μl of saline, a DMG-PEG dilutant (0.002 μg/μl), or with 1 μL of BNT162b2. Cells were stained with a viability dye (Zombie NIR Fixable Viability Kit, BioLegend, San Diego, California) and an antibody panel consisting of anti–CD63-FITC, anti–HLA-DR-PR, and anti–CD123-PerCP/Cy5.5 (Becton Dickinson, Franklin, New Jersey) using standardized published procedures.[1] Cells were counted by means of flow cytometry with the BD FACSCanto II Cell Analyzer (Becton Dickinson Immunocytometry Systems, San Jose, California) and analyzed with FlowJo Software (FlowJo LLC, Ashland, Oregon).

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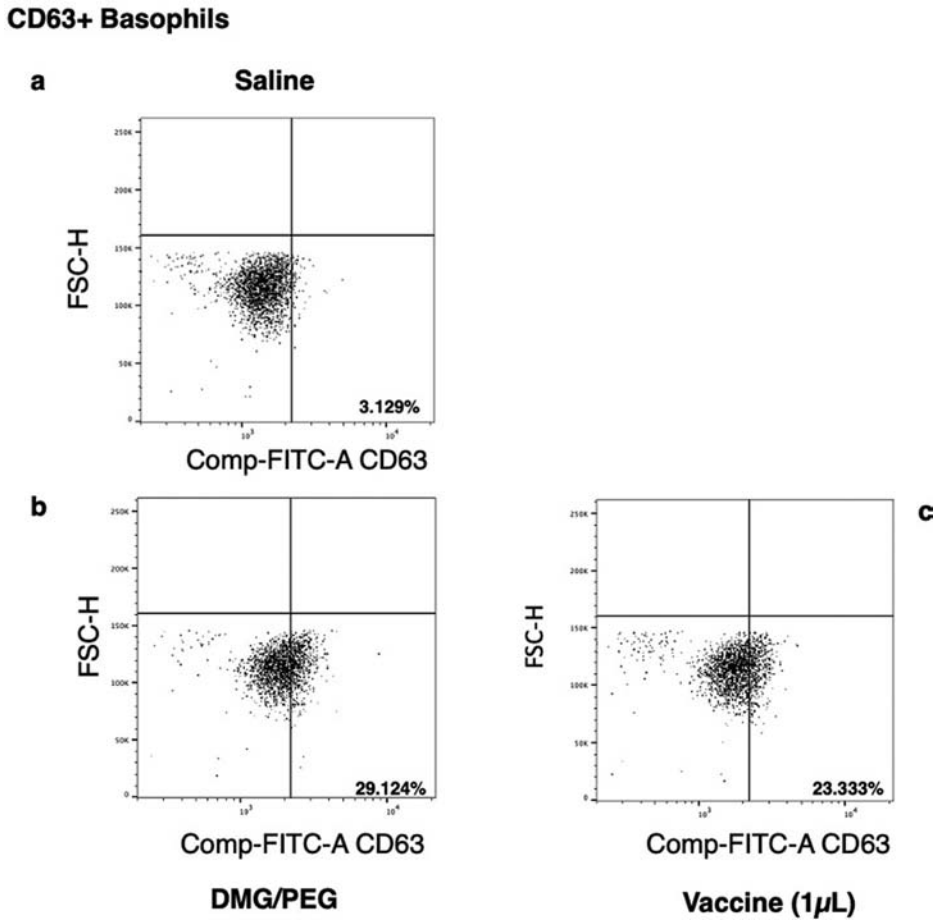

Figure 1. Basophil activation test result for gated basophil populations with the activation marker CD63+. Plots for (A) saline (control for background activation), (B) DMG-PEG, and (C) BNT162b2 vaccine. Comp-FITC-A CD63, compensated fluorescein isothiocyanate-A CD63; DMG-PEG, dimyristoyl glycerol-polyethylene glycol; FSC-H, forward scatter height.

Using the patient's sera, enzyme-linked immunosorbent assay was performed to detect anti-PEG antibodies. Enzyme-linked immunosorbent assays were developed with anti-PEG human-6.3-Immunoglobulin G (IgG) with a cutoff optical density (OD_{405}) of 0.4 and anti-PEG human-6.3-IgE with a cutoff OD_{405} of 0.2. Anti-PEG IgE and IgG standards were used (Academia Sinica, Taiwan).

The SPT result was interpreted as negative to BNT162b2, DMG-PEG, and polysorbate 80. Basophils were detectable in the patient's samples and activated basophils were gated as CD63-positive (CD63+), CD123-positive, and HLA-DR−negative. For blood stimulated with DMG-PEG 2000 or BNT162b2, 29.1% and 23.3% of basophils, respectively, were CD63+, compared with 3.129% in the saline control group (Fig 1). Samples of the patient's sera tested with anti-PEG human-6.3-IgG and anti-PEG human-6.3-IgE resulted in titers below cutoff values.

Polyethylene glycol is a vaccine stabilizer used in the Pfizer-BioNTech and Moderna mRNA COVID-19 vaccines and is thought to be a major contributing allergen.[2] It has never previously been included in approved vaccines, but it serves as an excipient in a number of medicines, foods, and cosmetics. Activation of the patient's basophils on exposure to the vaccine excipient PEG implicates PEG as a potential allergen. However, given the low anti-PEG titers, the reaction seems to be non-IgE- and non−IgG-mediated anaphylaxis. The tryptase from the index event was negative; however, negative tryptase after a case of anaphylaxis to the Pfizer vaccine has been described.[2] Skin prick testing performed on the patient to the vaccine, DMG-PEG 2000, and polysorbate 80 all had negative results. Although we did not test multiple molecular weights of PEG, there is evidence that PEG2000 (molecular weight 2000 Da) found in the vaccine can result in negative SPT despite clinical anaphylaxis to PEG.[2–4] Furthermore, higher molecular weight PEGs may have a lower reactivity threshold.[4]

Anaphylaxis to PEGylated compounds is unusual but has been reported in the literature, including 53 unique cases identified by Stone et al[3] from the Food and Drug Administration Adverse Event Reporting System between 1989 and 2017, and similarly, 37 cases identified by Wenande and Garvey[4] between 1977 and 2016. Case reports of suggested IgE-mediated hypersensitivity to PEG provide some insights; however, PEG-specific IgE is often not detectable, which may, in some circumstances, result from a lack of assay sensitivity.[4–7] In other cases, PEGylated lipid nanoparticles may activate host immune defense through non-IgE pathways such as Mas-related G protein-coupled receptor X2−mediated direct mast cell and basophil degranulation and complement activation−related pseudoallergy to PEG.[8,9]

Recent data reported the tolerability of a second dose COVID-19 mRNA vaccine with an antihistamine or steroid premedication in those with convincing immediate hypersensitivity reactions to the first dose.[10] This suggests a role for possible second or booster dose of mRNA vaccine or alternative Janssen COVID-19 vaccine under an allergist's supervision for those with vaccine-associated PEG hypersensitivity.

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Association of initial esophageal eosinophil counts with atopic dermatitis in patients with eosinophilic esophagitis

The estimated prevalence of atopic dermatitis (AD) in patients with eosinophilic esophagitis (EoE) ranges from 2% to 19%.[1] We hypothesized that the presence of AD is associated with increased severity of EoE, defined as an increased rate of food impaction, esophageal stricture, or subepithelial fibrosis on biopsy in a cohort of pediatric patients. We further hypothesized that eosinophil counts on endoscopy would be higher in patients with EoE and concomitant AD than in those without AD.

We performed an institutional review board–exempt retrospective chart review of patients with a diagnosis of EoE (identified by the International Classification of Diseases, Tenth Revision codes) seen in the Penn State Children's Hospital Allergy, Asthma and Immunology Clinic between January 1, 2016, and June 30, 2019, from existing databases of Research Electronic Data Capture (Vanderbilt University, Nashville, Tennessee). Of note, 8 patients seen in the gastroenterology clinic (but not yet seen in the allergy clinic) were also included in the study. A total of 273 charts were reviewed, and 77 charts were included with a confirmed diagnosis of EoE, defined as esophageal eosinophilia greater than or equal to 15 eosinophils per high-power field on esophageal biopsy with symptoms of esophageal dysfunction. The study excluded 196 patients not seen during the designated time period and patients who did not have a confirmed (but only suspected) diagnosis of EoE on esophageal biopsy. The prevalence of food impaction, esophageal stricture, and subepithelial fibrosis on biopsy was compared between cases of patients with EoE with AD and the control group of patients with EoE without AD, using logistic regression. Potential confounders and covariates were tested and adjusted for. A sensitivity analysis was performed. When applicable, data were analyzed with χ^2 test, with a P value of less than .05 considered significant. For peak eosinophil counts on biopsy, the Wilcoxon ranked sum test was used.

The age of patients ranged from 3 to 21 years (median, 13 years). Most patients were of male sex (57), with only 20 female patients. The patients were mainly White (57), with 11 Hispanic, 6 African American, and several minorities.

EoE symptom report is variable. A sensation of choking may not always result in objective episodes of food impaction or be well differentiated from dysphagia. We defined food impaction as physician-documented episodes of food impaction, noted in 12 (16%) of patients with EoE alone and 1 (6%) of patients with EoE and AD. Of 61 patients with EoE alone, 11 (18%) had vomiting, and of 16 patients with EoE and AD, 1 (6%) had vomiting. Many patients have compensatory eating behaviors to minimize the symptoms.[2]

Concomitant gastroesophageal reflux disease was found in 54 (70%) patients by the International Classification of Diseases, Tenth Revision codes. AD was found in 16 (21%) patients, asthma in 39 (51%) patients, allergic rhinitis in 49 (64%) patients, and immunoglobulin E–mediated food allergy in 22 (29%) patients. Subepithelial fibrosis on esophageal biopsy was found in 32 (42%) patients, food impaction in 13 (17%) patients, microabscesses in 31 (40%) patients, and esophageal strictures in only 1 (1.36%) patient. Microabscesses were found in 18 (46%) patients with asthma, 24 (49%) patients with allergic rhinitis, and 7 (44%) patients with AD. Excluding allergic rhinitis (P = .03), these results were not statistically significant. Of 16 patients with EoE and AD, subepithelial fibrosis was found in 4 (25%, P = .11) patients and food impaction in 1 (6.25%, P = .28) patient.

We did not find a higher incidence of food impaction, subepithelial fibrosis, and esophageal stricture in patients with EoE and concomitant AD. Asthma, allergic rhinitis, and immunoglobulin E–mediated food allergy were also not each associated with an increased EoE severity. Of 39 patients with asthma, 13 (33%) had subepithelial fibrosis, whereas 5 (13%) had food impaction. Of 49 patients with allergic

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