Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Biphasic anaphylaxis after first dose of messenger RNA coronavirus disease 2019 vaccine with positive polysorbate 80 skin testing result

Initial reports of anaphylaxis after the first dose of the Pfizer-BioNTech (Pfizer Inc, New York, New York; BioNTech SE, Mainz, Germany) vaccine suggested a case rate of 11.1 per million doses, but subsequent reports estimate a rate of 5 per million doses.[1,2] In a recent description of 21 anaphylaxis cases after the first dose of the Pfizer-BioNTech vaccine, there were no biphasic reactions.[3] We present the case of an individual who experienced suspected biphasic anaphylaxis after the first dose of the Pfizer-BioNTech coronavirus disease 2019 (COVID-19) vaccine.

A 42-year-old female nurse with depression and anxiety treated with bupropion but no previous atopic history or anaphylaxis presented for her first dose of the Pfizer-BioNTech COVID-19 vaccine at a nurse and paramedic staffed employee vaccination clinic in a major hospital. After 10 minutes from vaccination, she developed facial angioedema noted by multiple medical providers, sensation of throat closure, hoarse voice, and a pruritic rash on her neck and upper chest with no substantial injection site reaction. At the vaccination site, she was treated with oral diphenhydramine and 0.3 mg intramuscular epinephrine with symptom improvement. She was transported to the emergency department, where she had a heart rate of 108 bpm and blood pressure of 137/87 mm Hg. She was treated with 20 mg intravenous famotidine and 10 mg intravenous dexamethasone and observed for 6 hours without symptom recurrence. A tryptase drawn 90 minutes after symptom onset was elevated at 12.5 ng/mL (<11.5 ng/mL). She was discharged with an epinephrine autoinjector and initially did well, but the following evening (30 hours postvaccination), she developed recurrent tongue swelling (noted by husband), sensation of throat closing, eye puffiness, diaphoresis, and lightheadedness. She administered oral diphenhydramine and her epinephrine autoinjector with rapid improvement in her symptoms. She went back to the emergency department where providers noted resolution of tongue swelling but persistent periorbital edema. There was no rash. Her heart rate was 109 bpm, and her blood pressure was 121/74 mm Hg. She was treated with 10 mg intravenous dexamethasone, observed for 4 hours, and discharged with no subsequent symptom recurrence.

She was evaluated in an allergy clinic 3 weeks after her reaction. Further history revealed previous tolerance of polyethylene glycol (PEG)-containing medications (MiraLAX [Bayer, Leverkusen, Germany]). She had no known drug allergies or dermal fillers. Because of her marked systemic reaction, she underwent expanded skin testing.[4] Testing results to PEG, methylprednisolone sodium, methylprednisolone acetate, and polysorbate 20 were negative. Skin testing result to triamcinolone acetonide (containing polysorbate 80) was negative with a 40 mg/mL skin prick and 1:100 and 1:10 intradermals but result to a 1:1 intradermal was positive (Table 1). Additional testing results were positive to Refresh sterile eye drops (Allergan, Inc., Dublin, Ireland), negative to Prevnar-13 (Wyeth Pharmaceuticals, Philadelphia, Pennsylvania) (both containing polysorbate 80), and negative to the Pfizer-BioNTech vaccine (Table 1). A baseline serum tryptase was persistently elevated at 12.8 ng/mL, although spot urine measurements of mast cell mediators (leukotriene E4, 2,3-dinor-11beta-prostaglandin F2 alpha, and N-methylhistamine) were normal. KIT D816V mutation testing result on peripheral blood was negative but testing result for hereditary alpha tryptasemia was positive with an extra alpha tryptase copy number. She is avoiding the second dose of the Pfizer-BioNTech vaccine until an in-office challenge is performed.

Several aspects of this case deserve discussion. Biphasic anaphylaxis is well described but uncommon, occurring in approximately 3% of adults who develop anaphylaxis.[5] Risk factors for a biphasic reaction include previous anaphylaxis, unknown trigger, and delayed epinephrine administration, although these are variable among different study populations.[5] In adults, the estimated median time from exposure to the biphasic reaction is 15 hours.[6] Our case is unique in the fact that the patient had a biphasic reaction despite no history of allergy and prompt receipt of epinephrine during the initial reaction, although some symptoms may have been anxiety related. To the best of our knowledge, this is the first reported case of suspected biphasic anaphylaxis to the Pfizer-BioNTech vaccine.

Another interesting aspect is the positive polysorbate 80 skin test result. Polysorbate 80 is a large nonionic compound that is a widely used excipient in many oral and injectable medications, including the Janssen COVID-19 vaccine (Janssen Pharmaceuticals, Beerse, Belgium), but is not present in the messenger RNA (mRNA) COVID-19 vaccines. It is cross-reactive with PEG, another excipient thought to be the leading culprit in allergic reactions to the mRNA COVID-19 vaccines. Immunoglobulin E and non–immunoglobulin E-mediated mechanisms are implicated in polysorbate and PEG reactions.[7] Expert opinion suggests an algorithm using nonirritating concentrations for PEG and polysorbate testing in the evaluation of patients with possible anaphylaxis to the mRNA COVID-19 vaccines.[4] There has only been 1 report of immediate hypersensitivity from a polysorbate 80-containing vaccine (Gardasil [Merck & Co., Kenilworth, New Jersey]) with positive results to skin prick and intradermal testing to this vaccine.[8] It is plausible that our patient's reaction to the Pfizer-BioNTech vaccine was the result of PEG and polysorbate 80 cross-reactivity, which has been previously reported, albeit in patients with a positive PEG skin testing result.[9] Our patient's negative results to PEG and methylprednisolone skin tests may suggest against cross-reactivity, although an alternative explanation is that the PEG concentration used for skin testing was too low to elicit a positive reaction. Owing to institutional restrictions, intradermal testing to the Pfizer-BioNTech vaccine was unable to be performed, which would be the next step in evaluation. In addition, use of Refresh is nonstandardized and based on expert opinion without established nonirritating concentrations. The sensitivity and specificity of skin testing to the vaccine and its components are unknown as is the mechanism of reaction. More patients will have to be evaluated to elucidate this further.

A final interesting point is the patient's persistent tryptase elevation 3 weeks after her index reaction. Systemic mastocytosis and monoclonal mast cell activation syndrome were deemed less likely after her negative KIT mutation testing result. Nevertheless, genetic testing result for hereditary alpha tryptasemia was positive and may have contributed to her symptoms given its association with elevated basal serum tryptase and increased risk of severe anaphylaxis.[10]

Despite this case report, in the overwhelming majority of cases, the risk of morbidity and mortality from COVID-19 will far outweigh the risk associated with vaccination. Although more study is needed to determine the use of skin testing in the evaluation of vaccine reactions, the widespread vaccination of the global population is imperative in the control of the pandemic.

Disclosures: The authors have no conflicts of interest to report.
Funding: The authors have no funding sources to report.

Table 1
Skin Testing Results

Steps[a]	PEG 3350 MiraLAX (170 mg/mL)	Methylprednisolone acetate (40 mg/mL)	Control Methylprednisolone sodium (40 mg/mL)	Polysorbate 20 Polysorbate 20 (0.5 mg/mL)	Polysorbate 80 Triamcinolone acetonide (40 mg/mL)	Refresh eye drops	Prevnar 13 vaccine	mRNA COVID-19 vaccine Pfizer-BioNTech (lot number ER8731)
Step 1	1:100 SP (0)	1:1 SP (0)	1:1 SP (0)	1:1 SP (0)	1:1 SP (0)	1:1 SP (0)	1:10 SP (0)	1:1 SP (0)
Step 2	1:10 SP (0)	1:100 ID (0)	1:100 ID (0)		1:100 ID (0)	1:10 ID (3 × 3 wheal, 7 × 7 flare)	1:100 ID (0)	
Step 3	1:1 SP (0)	1:10 ID (0)	1:10 ID (0)		1:10 ID (0 wheal, 4 × 4 flare)			
Step 4					1:1 ID (3 × 3 wheal, 8 × 8 flare)			

Abbreviations: COVID-19, coronavirus disease 2019; ID, intradermal; PEG, polyethylene glycol; mRNA, messenger RNA; SP, skin prick.
[a]Controls done before testing include control prick (0), histamine 6 mg/mL SP (3 × 3 flare).

Mitchell M. Pitlick, MD*
Miguel A. Park, MD*
Alexei Gonzalez-Estrada, MD†
Sergio E. Chiarella, MD*
* *Division of Allergic Diseases*
Mayo Clinic
200 First St SW Rochester, MN, 55905,
† *Division of Pulmonary, Allergy, and Sleep Medicine*
Mayo Clinic
Jacksonville, Florida
Chiarella.sergio@mayo.edu

References

1. CDC COVID-19 Response Team, Food and Drug Administration. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine—United States, December 14-23, 2020. *MMWR Morb Mortal Wkly Rep*. 2021;70(2):46–51.
2. 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;325:1101–1102.
3. Shimabukuro T, Nair N. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine. *JAMA*. 2021;325(8):780–781.
4. Banerji A, Wichner PG, Saf R, 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(4):1423–1437.
5. Lee S, Sadosty AT, Campbell RL. Update on biphasic anaphylaxis. *Curr Opin Allergy Clin Immunol*. 2016;16(4):346–351.
6. Ko BS, Kim WY, Ryoo SM, et al. Biphasic reactions in patients with anaphylaxis treated with corticosteroids. *Ann Allergy Asthma Immunol*. 2015;115(4). 312-216.
7. Castells MC, Phillips EJ. Maintaining safety with SARS-CoV-2 vaccines. *N Engl J Med*. 2021;384(7):643–649.
8. Badiu I, Guena M, Heffler E, Rolla G. Hypersensitivity reaction to human papillomavirus vaccine due to polysorbate 80. *BMJ Case Rep*. 2012;2012. bcr0220125797.
9. Stone Jr CA, Liu Y, Relling MV, et al. Immediate hypersensitivity to polyethylene glycols and polysorbates: more common than we have recognized. *J Allergy Clin Immunol Pract*. 2019;7(5):1533–1540.
10. Lyons JJ, Chovanec J, O'Connel MP, et al. Heritable risk for severe anaphylaxis associated with increased α-tryptase-encoding germline copy number at TPSAB1. *J Allergy Clin Immunol*. 2021;147(2):622–632.

Detection of neutralizing anti–severe acute respiratory syndrome coronavirus 2 antibodies in patients with common variable immunodeficiency after immunization with messenger RNA vaccines

Check for updates

Common variable immunodeficiency (CVID) is a rare disorder, occurring in approximately 2 to 4 per 100,000 individuals in the general population. Nevertheless, it is the most common symptomatic primary immunodeficiency disorder in adults and may account for a substantial proportion of patients in specialized immunology clinics. The cause is unknown; diagnosis relies on multiple criteria because no single clinical manifestation or laboratory test can aid in recognizing this entity.[1] Specifically, CVID may be diagnosed in case of a marked decrease of immunoglobulin G (IgG) (at least 2 SD below the mean for age) and a marked decrease in IgM or IgA, in addition to the following criteria: (1) onset of immunodeficiency at greater than 2 years of age; (2) absent isohemagglutinins and poor response to vaccines; and (3) exclusion of other possible causes of hypogammaglobulinemia.[1] Antibody production is always impaired in CVID, as a result of primary B-cell dysfunction or from lack of T cell help for antibody production.[1]

The current pandemic of the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represents an unprecedented challenge for health care systems across the world,[2] but the ongoing global mass vaccination against SARS-CoV-2 may help reduce the hospital burden worldwide. Patients with CVID, however, may not be included into the vaccination programs because of the common perception that they are not responsive to vaccination.[1] In countries such as Italy, where general practitioners are in charge of the recruitment of "fragile" patients into vaccination programs, it is paramount to address the issue of the effectiveness of COVID-19 vaccines in patients with primary immunodeficiency, also considering the low awareness on this peculiar group of diseases among physicians not specializing in clinical immunology.[3]

Therefore, to establish whether SARS-CoV-2 vaccination may be meaningful in individuals with CVID, we investigated whether these patients could generate protective antibodies against SARS-CoV-2 after administration of messenger RNA (mRNA) vaccines[4] and compared the outcome in healthy subjects from hospital staff undergoing COVID-19 vaccination.

A total of 5 patients (4 females, 1 male; median age, 54 years) with CVID (median age at diagnosis, 35 years) on monthly intravenous immunoglobulin replacement therapy agreed to receive an mRNA vaccine.[4] Serum SARS-CoV-2 antibodies were measured in all

Disclosures: The authors have no conflicts of interest to report.
Funding: The authors have no funding sources to report.