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**Biphasic anaphylaxis after first dose of mRNA COVID-19 vaccine with positive polysorbate 80 skin testing**

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Initial reports of anaphylaxis following the first dose of the Pfizer-BioNTech vaccine suggested a case rate of 11.1 per million doses, but subsequent reports estimate a rate of 5 per million doses.<sup>1,2</sup> In a recent description of 21 anaphylaxis cases following the first dose of the Pfizer-BioNTech vaccine there were no biphasic reactions.<sup>3</sup> We present the case of an individual who experienced suspected biphasic anaphylaxis following the first dose of the Pfizer-BioNTech COVID-19 vaccine.

A 42 year old female nurse with depression and anxiety treated with bupropion but no prior atopic history or anaphylaxis presented for her first dose of the Pfizer-BioNTech COVID-19 vaccine at a nurse/paramedic staffed employee vaccination clinic in a major hospital. Ten minutes after 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 significant 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, 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 post-vaccination) 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 allergy clinic 3 weeks after her reaction. Further history revealed prior tolerance of polyethylene glycol (PEG) containing medications (MiraLAX). She had no known drug allergies or dermal fillers. Because of her significant systemic reaction, she underwent expanded skin testing.<sup>4</sup> Testing to PEG, methylprednisolone sodium, methylprednisolone acetate, and polysorbate 20 were negative. Skin testing to triamcinolone acetonide (polysorbate 80 containing) was negative with a 40 mg/mL skin prick and 1:100 and 1:10 intradermals, but a 1:1 intradermal was positive (Table 1). Additional testing was positive to Refresh sterile eye drops, negative to Prevnar-13 (both polysorbate 80 containing) 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 E<sub>4</sub>, 2,3-dinor11 $\beta$ -prostaglandin F<sub>2</sub>  $\alpha$ , and N-methylhistamine) were normal. KIT D816V mutation testing on peripheral blood was negative, but testing for hereditary alpha tryptasemia (H $\alpha$ T) 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.<sup>5</sup> Risk factors for a biphasic reaction include prior anaphylaxis, unknown trigger, and delayed epinephrine administration, although these are variable among different study populations.<sup>5</sup> In adults, the estimated median time from exposure to the biphasic reaction is 15 hours.<sup>6</sup> Our case is unique in the fact that the patient had a biphasic reaction despite no prior allergic history and prompt receipt of epinephrine during the initial reaction, although some symptoms may have been

anxiety-related. To 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. Polysorbate 80 is a large non-ionic compound that is a widely used excipient in many oral and injectable medications, including the Janssen COVID-19 vaccine, but is not present in the 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. IgE and non-IgE mediated mechanisms are implicated in polysorbate and PEG reactions<sup>7</sup>. Expert opinion suggests an algorithm utilizing non-irritating concentrations for PEG and polysorbate testing in the evaluation of patients with possible anaphylaxis to the mRNA COVID-19 vaccines.<sup>4</sup> There has only been one report of immediate hypersensitivity from a polysorbate 80 containing vaccine (Gardasil) with positive skin prick and intradermal testing to this vaccine.<sup>8</sup> 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 positive PEG skin testing.<sup>9</sup> Our patient's negative 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. Due to institutional restrictions, intradermal testing to the Pfizer-BioNTech vaccine was unable to be performed, which would be the next step in evaluation. Additionally, use of Refresh is non-standardized and based on expert opinion without established non-irritating concentrations. The sensitivity and specificity of skin testing to 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 negative KIT mutation testing. However, genetic testing for HαT was positive and may have contributed to her symptoms given its association with elevated basal serum tryptase and increased risk of severe anaphylaxis.<sup>10</sup>

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. While more study is needed to determine the utility of skin testing in the evaluation of vaccine reactions, the widespread vaccination of the global population is imperative in the control of the pandemic.

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Table 1: Skin Testing Results

| Step<br>s* | PEG 3350                          |                                              | Control                                     | Polysorb<br>ate 20                   | Polysorbate 80                                        |                                                |                              | mRNA<br>COVID-<br>19<br>vaccine                 |
|------------|-----------------------------------|----------------------------------------------|---------------------------------------------|--------------------------------------|-------------------------------------------------------|------------------------------------------------|------------------------------|-------------------------------------------------|
|            | Miral<br>ax<br>(170<br>mg/m<br>L) | Methylpredniso<br>lone acetate (40<br>mg/mL) | Methylpredniso<br>lone sodium (40<br>mg/mL) | Polysorb<br>ate 20<br>(0.5<br>mg/mL) | Triamcinol<br>one<br>acetone<br>nide<br>(40<br>mg/mL) | Refre<br>sh<br>Eye<br>Drops                    | Prev<br>ar 13<br>vaccin<br>e | Pfizer-<br>BioNTe<br>ch<br>(Lot#<br>ER8731<br>) |
| Step<br>1  | 1:100<br>SP (0)                   | 1:1 SP (0)                                   | 1:1 SP (0)                                  | 1:1 SP (0)                           | 1:1 SP (0)                                            | 1:1 SP<br>(0)                                  | 1:10<br>SP (0)               | 1:1 SP<br>(0)                                   |
| Step<br>2  | 1:10<br>SP (0)                    | 1:100 ID (0)                                 | 1:100 ID (0)                                |                                      | 1:100 ID<br>(0)                                       | 1:10<br>ID<br>(3x3<br>wheal<br>, 7x7<br>flare) | 1:10<br>ID (0)               |                                                 |
| Step<br>3  | 1:1 SP<br>(0)                     | 1:10 ID (0)                                  | 1:10 ID (0)                                 |                                      | 1:10 ID (0<br>wheal, 4x4<br>flare)                    |                                                |                              |                                                 |
| Step<br>4  |                                   |                                              |                                             |                                      | 1:1 ID (3x3<br>wheal, 8x8<br>flare)                   |                                                |                              |                                                 |

SP: skin prick; ID: Intradermal; PEG: polyethylene glycol

\* Controls done prior to testing include control prick (0), histamine 6 mg/mL SP (3x3 flare)