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SHORT COMMUNICATION

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Biphasic anaphylaxis after exposure to the first dose of Pfizer-BioNTech COVID-19 mRNA vaccine

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Abstract

In the setting of a coronavirus disease 2019 (COVID-19) global pandemic and increased disease burden, vaccination has become one of the major solutions. With the increase in vaccination numbers worldwide, it is important to stay vigilant to the potential side effects and life-threatening complications of such vaccines. We report the case of a 30-year-old male with a biphasic allergic reaction post messenger (mRNA) Pfizer-BioNTech COVID-19 vaccination. Several reports of allergic reactions have been cited in the literature after the administration of the mRNA Pfizer-BioNTech COVID-19 vaccine. It is important to keep a high index of suspicion in severe anaphylactic cases as some patients may have a recurrence of symptoms after discharge. It is crucial to acknowledge the potential risk of anaphylaxis in select individuals and have the appropriate measures in place to deal with adverse events. In case of severe symptoms, the administration of epinephrine is advised to prevent the development of a delayed biphasic anaphylactic reaction.

KEYWORDS

coronavirus, disease control, SARS coronavirus, vaccines/vaccine strains, virus classification

1 | INTRODUCTION

As of May 21, 2021, a total of 165 158 285 cases of coronavirus disease 2019 (COVID-19) and 3 425 017 associated deaths have been reported worldwide. Serious complications during and following infection have been seen and reported including acute respiratory distress syndrome, stroke, pulmonary embolism, and death.

On December 11, 2020, the Food and Drug Administration (FDA) authorized the emergency use of the two-dose Pfizer-BioNTech COVID-19 vaccine. Globally, the latest vaccination rate is 6 469 833 doses per day, on average, with 41.7 million individuals having received the first dose of the vaccine.[1] As vaccination started in several countries, adverse events related to the vaccine were registered through the Vaccine Adverse Event Reporting System (VAERS). About 175 cases of severe allergic reactions were submitted for review thus far.[2] The Center for Disease Control (CDC) identified 21 case reports of anaphylaxis that met the Brighton Criteria.[3]

We report the first case of biphasic anaphylaxis after exposure to the Pfizer-BioNTech COVID-19 vaccine.

2 | CASE PRESENTATION

2.1 | Day 1

Patient took the messenger RNA (mRNA) Pfizer-BioNTech COVID-19 vaccine on February 15, 2021. This is a case of a 30-year-old gentleman, a registered nurse at our institution, previously healthy, known to have allergies to meperidine, amocixillin-clavulonate acid, pollen, and dust mites, who presented to the Emergency Department (ED) after few minutes of receiving the first dose of the COVID-19 Pfizer-BioNTech vaccine with a full body and face diffuse maculopapular rash.

His symptoms were associated with urticaria, diaphoresis, tachycardia, and tachypnea. The patient also reported dysphagia and

palate pruritis. No dysphonia and no dyspnea. The otolaryngology team was contacted for an assessment of the airway.

On physical examination, the patient was alert oriented and cooperative, and hemodynamically stable. He was breathing comfortably on room air, in no respiratory distress, and no stridor. There was no desaturation and facial asymmetry. No lip or eyelid swelling. On examination of the oral cavity, the uvula was midline, nonedematous, and the tongue was nonedematous as well.

Flexible Fiberoptic Laryngoscopy (FFL) through the left nasal cavity revealed a tight nasal cavity with inferior turbinate edema and a prominent base of the tongue, however, not obstructing the inlet of the airway. The epiglottis unremarkable, as well as the bilateral valleculae and pyriform sinuses. Bilateral arytenoids were erythematous and edematous, but the bilateral vocal cords were mobile with complete closure

In the ED, he later received diphenhydramine 25 mg intravenously (iv) once and hydrocortisone 50 mg iv once with rash resolution. The patient was monitored in ED for 6 h, and our scope was repeated then. Resolution of the edema at the level of the arytenoid and base of the tongue was evident, along with all his other symptoms. He was discharged home in stable condition. The patient was discharged on diphenhydramine-paracetamol (1 tablet per day if needed for urticaria) along with prednisone PO 50 mg daily for 5 days.

2.2 | Day 2

The patient had an episode of rash, pruritis, dyspnea, and diaphoresis at home. Symptoms resolved after the patient took prednisone 50 mg orally at home. He did not present to the ED due to the resolution of his symptoms.

2.3 | Day 3

The patient reported back to work, however, he experienced sudden onset of rash followed by urticaria, diaphoresis, severe chills, and dysphagia. We were called again for an airway assessment. He took prednisone 50 mg PO as the rash appeared with no improvement. Intravenous access was secured. He was given diphenhydramine 25 mg iv, dexamethasone 8 mg iv, and hydrocortisone sodium succinate 250 mg iv once. The patient was then transferred to the ED.

He was alert-oriented and cooperative, hemodynamically stable, however, using accessory abdominal muscles to breathe. No desaturation, SpO_2 was 100% but the patient was tachypneic without stridor. FFL during assessment showed an unremarkable exam with no evidence of edema or erythema along the upper airway. The patient was given in ED a second dose of diphenhydramine 25 mg iv once, dexamethasone 8 mg, and was kept for monitoring.

On repeat assessment 3 h later, the patient was found to have mild swelling of the eyelids and lips with evidence of base of tongue edema and arytenoid erythema on FFL. The patient was still symptomatic with severe recurring pruritis, dyspnea, dysphagia, and sensation of throat closing up. The patient was given a third dose of diphenhydramine 25 mg iv, epinephrine IM 0.3 mg once, and was started on hydrocortisone sodium succinate 100 mg every 8 h. Repeat assessment and FFL after another 3 h showed resolution of all symptoms. The only remaining finding was the lagging arytenoid erythema without any evidence of airway compromise.

2.4 | Day 4

The patient was hospitalized for observation. On Day 4 of events, the patient was in no acute distress with no recurrence of his symptoms. Edema had resolved with no audible stridor, no tachypnea, or chills. COVID-19 polymerase chain reaction was taken and found to be negative, to rule out any hyper-inflammatory reaction to the vaccine.

3 | DISCUSSION

Allergic reactions to vaccination are common especially with the increase in administration worldwide. Reactions are mainly IgE mediated and immediate-type allergic reactions to protein components of the vaccine.[4] Patients with allergies to vaccine components should be evaluated by an allergist. A thorough history taking is needed to determine the nature and timing of the reaction to the vaccine in question and its constituents.

Immediate reactions, comparable to anaphylaxis, have been described shortly after administration of the first dose of Pfizer-BioNTech COVID-19 mRNA vaccine. Such reactions have been reported to occur at a rate of 11.1 per million doses of the vaccine.[2] Hypersensitivity events were reported with a lower incidence (0.63%) during the clinical trials for vaccine development due to the exclusion of individuals with a previous history of severe adverse reactions to vaccine products.[5]

Allergic reactions to vaccines have been widely described, for instance, the trivalent influenza vaccine has a postadministration reaction rate of 1.35 per million doses.[6] Confirmed allergic reactions to vaccines are not usually due to active ingredients but to the excipients added for the purpose of stabilizing and protecting the vaccine while eliciting a stronger immune response.[7] The Pfizer-BioNTech vaccine has been formulated with polyethylene glycol (PEG) for the purpose of stabilizing the lipid particle containing the virus mRNA. PEG has never been used in vaccines previously, however, there is cross-reactivity with polysorbate used in multiple vaccines (such as Influenza, Hepatitis B, etc.) and drugs (Amiodarone and many anti-neoplastic medications). It was hypothesized that previous exposure to polysorbate might explain the allergic reaction to the administration of the Pfizer-BioNTech COVID-19 mRNA vaccine.[8] This cross-reactivity between PEG and polysorbate is proportional to PEG molecular weight, with PEG-IgG exhibiting a higher affinity to PEG molecules with molecular weights above 1000.[8] To note that our patient had taken the Influenza vaccine earlier that year.

Of the 21 identified cases of anaphylaxis to the COVID-19 Pfizer-BioNTech vaccine from the CDC, the most common symptoms at presentation were urticaria, angioedema, rash, and sensation of throat closure.[3]

Similarly, the Moderna COVID-19 vaccine is an mRNA vaccine as well and has been associated with allergic side effects after administration. The literature cites 10 cases of anaphylaxis after administration of the first 4 041 396 doses at an estimated rate of 2.5 cases per million doses administered.[9] No reports of biphasic anaphylaxis after any of the two mRNA COVID-19 vaccines were encountered during our literature review.

Biphasic anaphylaxis is characterized by an initial onset of allergy symptoms with subsequent complete resolution. This symptom-free period is then followed by subsequent recurrence of symptoms without re-exposure to culprit allergen.[10] The duration of the symptom-free period separating both reactions vary between 1 and 78 h.[11]

The pathogenesis of biphasic anaphylaxis is still not clear due to the rarity of this entity. Some suggest that the late synthesis of Platelet Activating Factor (PAF) was responsible for the second delayed reaction. PAF is already established to play an important role in murine anaphylaxis pathogenesis and is upregulated by TNF-alpha expression. This theory is further supported by the inhibition of the late-phase response by TNF-alpha inhibition.[12]

Other studies suggest that the delayed phase reaction is more likely due to uneven antigen absorption. This polyphasic absorption causes the body to be exposed and react to the allergen multiple times and stimulating biphasic anaphylaxis.[13] This is mostly true of orally absorbed allergens, however, intramuscular route administration can result in biphasic absorption if precipitation occurs at the injection site.[14]

Possible risk factors for the development of a biphasic reaction include severe presenting symptoms such as hypotension[15] and inadequate or delayed administration of epinephrine during the initial encounter.[16] This might explain why our patient developed a biphasic allergic reaction, as he did not receive epinephrine on Day 1. Glucocorticoids and antihistamines have not been shown to significantly reduce the incidence of symptom recurrence in these patients.[16,17]

4 | CONCLUSION

It is highly important to differentiate allergic from nonallergic reactions following vaccine administration. In that light, it is crucial to acknowledge the potential risk of anaphylaxis in select individuals and have the appropriate measures in place to deal with adverse events. In case of anaphylaxis to Pfizer-BioNTech COVID-19mRNA vaccine, it is essential to provide adequate symptomatic and diagnostic management. In case of severe symptoms, the administration of epinephrine is advised to prevent the development of a delayed biphasic anaphylactic reaction.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest.

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REFERENCES

1. Randall T, et al., More Than 193 Million Shots Given: COVID-19 Tracker. 2021: Bloomberg.
2. CDC and FDA. 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.
3. Shimabukuro T, Nair N. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine. *JAMA*. 2021;325:780.
4. Chung EH. Vaccine allergies. *Clin Exp Vaccine Res*. 2014;3(1):50-57.
5. Banerji A, Wickner PG, Saff R, et al. mRNA vaccines to prevent COVID-19 disease and reported allergic reactions: current evidence and suggested approach. *J Allergy Clin Immunol Pract*. 2020;9:1423-1437.
6. McNeil MM, Weintraub ES, Duffy J, et al. Risk of anaphylaxis after vaccination in children and adults. *J Allergy Clin Immunol*. 2016; 137(3):868-878.
7. Stone CA Jr., Rukasin C, Beachkofsky TM, Phillips EJ Jr. Immune-mediated adverse reactions to vaccines. *Br J Clin Pharmacol*. 2019; 85(12):2694-2706.
8. Stone CA Jr, 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.
9. CDC COVID-19 Response Team. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Moderna COVID-19 Vaccine. *MMWR Morb Mortal Wkly Rep*. 2021;70:46-51.
10. Lieberman P. Biphasic anaphylactic reactions. *Ann Allergy Asthma Immunol*. 2005;95(3):217-226.
11. Pourmand A, Robinson C, Syed W, Mazer-Amirshahi M. Biphasic anaphylaxis: a review of the literature and implications for emergency management. *Am J Emerg Med*. 2018;36(8):1480-1485.
12. Vadas P, Gold M, Perelman B, et al. Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. *N Engl J Med*. 2008;358(1): 28-35.
13. Lee JM, Greenes DS. Biphasic anaphylactic reactions in pediatrics. *Pediatrics*. 2000;106(4):762-766.
14. Greenblatt DJ, Shader RI, MacLeod SM, Sellers EM, Franke K, Giles HG. Absorption of oral and intramuscular chlordiazepoxide. *Eur J Clin Pharmacol*. 1978;13(4):267-274.
15. Shaker MS, Wallace DV, Golden D, et al. Anaphylaxis-a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. *J Allergy Clin Immunol*. 2020;145(4):1082-1123.
16. Liu X, Lee S, Lohse CM, Hardy CT, Campbell RL. Biphasic reactions in emergency department anaphylaxis patients: a prospective cohort study. *J Allergy Clin Immunol Pract*. 2020;8(4):1230-1238.
17. Alqurashi W, Ellis AK. Do corticosteroids prevent biphasic anaphylaxis? *J Allergy Clin Immunol Pract*. 2017;5(5):1194-1205.

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