Anaphylaxis after Moderna COVID-19 vaccine

Therapeutic Advances in Vaccines and Immunotherapy

2021, Vol. 9: 1–6

DOI: 10.1177/25151355211048418

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***Abstract*:** The authors of this article report on a case of a patient who presented to the emergency department (ED) in anaphylaxis after receiving the Moderna® COVID-19 vaccine. The patient was hypoxic, with diffuse wheezing bilaterally to auscultation, flush skin, swollen face, and the feeling of her throat closing. Anaphylaxis can have wide range of presentation, the key is recognizing the symptoms and treating early. The incidence of anaphylaxis from COVID-19 vaccine is not well documented to date.

Keywords: COVID-19 vaccine, anaphylaxis

Received: 5 June 2021; revised manuscript accepted: 3 September 2021.

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Introduction

The Moderna COVID-19 vaccine along with the other mRNA vaccines use a process called transfection in which nucleic acids are artificially introduced into the cells. This then drives the production of antibodies against COVID-19. The process uses chemical compounds to surround the mRNA. These compounds allow the entire structure to pass through the cellular membrane of our cells.[1] Once the structure (Figure 1) is inside the cell, the mRNA binds to ribosomes and is translated into the COVID-19 spike protein. Each protomer in the trimeric spike has 22 glycosylation sites,[2] normally exists in a metastable, prefusion conformation; once the virus interacts with the host cell, extensive structural rearrangement of the S protein occurs, allowing the virus to fuse with the host cell membrane.[3] The protein is then transported to the cell surface where our immune cells form a complex with this protein initiating the start of our body's natural immune response against the spike protein. The end results are antibody production similar to what occurs during a natural COVID-19 infection.[4-6]

The vaccination process with Moderna COVID-19 vaccine is a two-dose intramuscular (IM) injection series that is administered 1 month apart. The efficacy after both doses was 94.1% in preventing symptomatic laboratory COVID-19 in Phase-III clinical trials. In the vaccine and placebo groups, the frequency of serious adverse events was 1%. However systemic reactions were reported to be higher in vaccine recipients than in those who received placebo (81.9% vs 71.9% after dose 2). The reactions among vaccine recipients ranged from local injection site reaction reported at 9.1%, systemic adverse reaction reported at 16.6%. On December 18, 2020, when the Food and Drug Administration issued an Emergency Use Authorization for Moderna COVID-19 vaccine, there were no cases of anaphylaxis reported.[7] Anaphylaxis can lead to death if not diagnosed and treated promptly. Previous studies have noted that not only is anaphylaxis under-recognized but is also under-treated, which has led to preventable fatalities. Understanding the symptoms that make the diagnoses of anaphylaxis more likely will lead to reduction in mortality in patient with anaphylaxis. The National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network have defined anaphylaxis as being the likely diagnosis when any one of the three criteria below are met (Figure 2).[8]

1. Skin, mucosal tissue symptoms acutely after allergen exposure; plus A) and/or B)
   - Respiratory symptoms, such as, wheezing and stridor.
   - Reduced blood pressure or end-organ dysfunction.

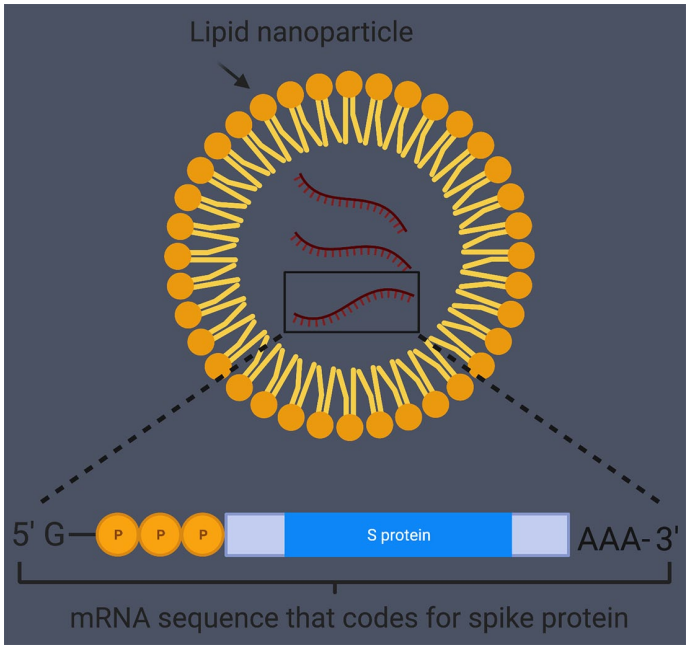

Figure 1. Schematic depicting lipid-coated mRNA sequence that codes for COVID-19 spike protein used in Moderna vaccine. Created with biorender.com.

2. Two or more of the following.
- Skin or mucosal symptoms.
- Respiratory compromise.
- Decreased blood pressure.
- GI symptoms such as diarrhea.

3. Finally signs of cardiovascular shock after exposure to an allergen.
- For infants, children, and adults, this is defined as >30% decrease in systolic blood pressure from baseline.
- For adults, it also includes a systolic blood pressure (for 50 kg, a 0.5 mg dose can be used).

After the diagnosis of anaphylaxis is made, prompt treatment must be initiated because a delay of even a few minutes can lead to hypoxia or death. The first-line treatment and only known medication to decrease mortality in anaphylaxis is epinephrine. The injection should be administered IM in the vastus lateralis muscle, located in the medial lateral aspect of the thigh. Dosing is weight based. The pediatric dose is 0.01 mg/kg of (1:1000 concentration). For children 10–25 kg, a 0.15 mg auto injector can be used. For children 25–50 kg, a .03 mg autoinjector can be used, and for patients >50 kg, a 0.5 mg dose can be used. This dosing can be repeated every 5–10 minutes as necessary for symptomatic improvement. Epinephrine has both alpha-adrenergic and beta-adrenergic stimulation, which is needed to counteract the distributive shock properties of anaphylaxis. Alpha1-stimulation increases peripheral vascular resistance, increases vasoconstriction, and decrease mucosal edema. Beta1-stimulation increases cardiac inotropy and chronotropy. Beta2-stimulation has the most important affect, it stabilizes mast cells and basophils which are responsible for the cascade chain reaction that leads to anaphylaxis, along with inducing bronchodilation.

The next step in the management of a patient with anaphylaxis follows the ABC algorithm of airway, breathing, and circulation. All patients should be placed on supplemental oxygen to maintain adequate oxygen saturation, in preparation for airway management a non-rebreather should be used. Patients with bronchospasm or wheezing should be given a trial of nebulized beta-agonists. Anaphylaxis is a special type of distributive shock thus patients should have two

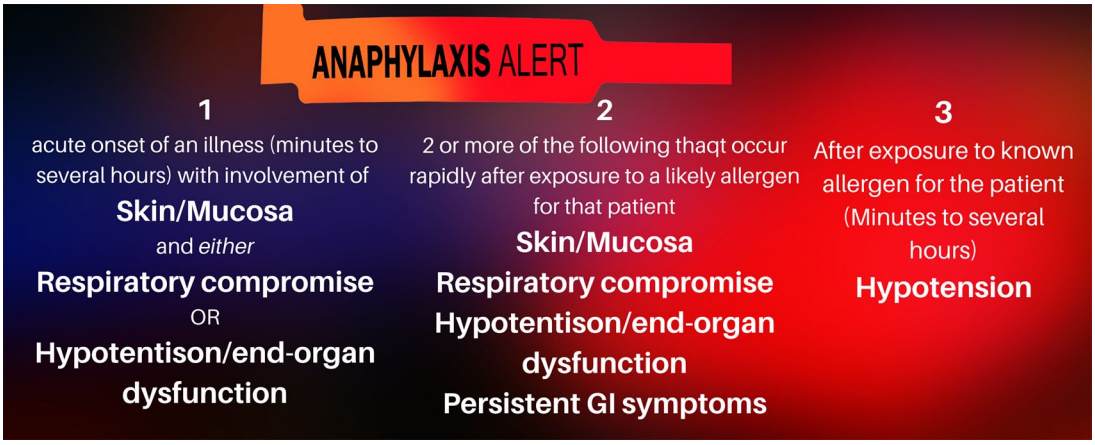

Figure 2. Anaphylaxis criteria.

large bore intravenous (IV) lines in place and infused with appropriate normal saline bolus. Once the administration of epinephrine has taken place and critical actions involving ABCs has been initiated second-line adjuncts can be given. These adjuncts included antihistamines H1, H2, and glucocorticoids. H1—anti-histamines mechanism acts to improve cutaneous symptoms including urticaria, pruritus, and angioedema. H2—anti-histamines work synergistically with H1 medications to relieve cutaneous symptoms. Glucocorticoids act to suppress the body's overall immune response and thereby decreasing length of symptoms.[9] Based on current research, corticosteroids, are thought to have no role in acute management of anaphylaxis. The onset for the effect of corticosteroids in too slow and would not be helpful in preventing severe outcomes, such as cardiac arrest or death.[10] There is no strong evidence for or against corticosteroid use in anaphylaxis cases, but there is no evidence of adverse outcomes as a result of corticosteroid use in the emergency treatment of anaphylaxis.[11]

The disposition for these patients depends on their response to treatment. Consensus guidelines vary and suggest that patients who experience a complete resolution of symptoms can be discharged home after a 4- to 8-h observation period. Patients who may require extended observation periods or admission include patients who are hypotensive, have that require any of the following: 1. Hypotension, airway involvement or protracted anaphylaxis; 2. Patients who have received two or more doses of IM epinephrine or received IV epinephrine; and 3. finally, patients who have inadequate outpatient social support.[9]

Case presentation

A 45-year-old female with a past medical history of asthma presents to the emergency department (ED) throat swelling, facial swelling, bilateral wheezing, and flushing of her skin after receiving Moderna COVID-19 vaccine. The symptoms started approximately 10 min after the vaccine was given. The first symptom she noticed was flushing of her skin, then abnormal throat sensation, which progressed to bilateral wheezing. She was immediately brought to the ED. On initial assessment, she was in respiratory distress, oxygen saturation 92% on room air, with diffuse wheezing bilaterally. She also endorsed she felt like her throat was "closing up" and was noted to have flushing of the skin and swelling of her face. She was immediately given 0.3 mg IM epinephrine in her left lateral thigh. Non-rebreather mask was placed for oxygen supplementation. IV access was obtained, patient was given 50 mg of diphenhydramine, 20 mg of famotidine, 125 mg of methylprednisone, and 1 L normal saline bolus. She was also placed on breathing treatment and given 9 mL albuterol ipratropium combination. Patient's overall status improved after approximately 5 minutes. She then began to complain of epigastric pain and nausea. She was given 4 mg of ondansetron, at which time the patient began to endorse extreme cramping of her neck and shoulder muscles. On examination, the patient's neck was held in a flexed position and patient's eyes remained shut. Patient was given 1 g of methocarbamol, and 0.25 of lorazepam, with resolution of symptoms. After approximately 15 min, all symptoms had resolved, and the patient was feeling much better.

The patient stated she had not received any nonsteroidal anti-inflammatory drugs (NSAIDs) or other medication, exercised, or drank alcohol prior to vaccination. She stated that she was up-to-date on her immunizations and received the yearly flu vaccine. She stated that her asthma has been under control for the past year and that she has never had an allergic reaction in the past. Besides having asthma and allergies, the patient is otherwise healthy, denies recent fever, chills, cough, chest pain, diarrhea, hematuria, dysuria, or recent travels. Along with asthma, the patient is hypersensitive to sulfur drugs and codeine. The patient's symptoms were not typical for other emergent causes of shortness of breath such as angioedema, panic attack, laryngeal edema, urticaria, pneumonia, foreign body obstruction, anaphylactoid reaction, acute coronary syndrome, pulmonary embolism, or anemia.

The patient was admitted for a 23-h observation. She remained asymptomatic during the observation period. During admission, she tested negative for COVID-19, chest radiograph demonstrated no acute findings, and all laboratory evaluation were within normal limits. The patient was advised that she should not receive the second dose of the Moderna COVID-19 vaccine until being cleared an allergist/immunologist. The patient was told to follow-up with her

primary care doctor and undergo an allergy workup specifically testing for polyethylene glycol (PEG), a component of the mRNA vaccines known to cause anaphylaxis. PEG is frequently associated with severe anaphylaxis. However, not all those who are allergic to PEG will have severe or even fatal anaphylaxis. The Moderna vaccine also contains trometamine, which could have been the cause of the patient's reaction, rather than the PEG. It is important to note that although this case presented as anaphylaxis to the ED, definitive allergy testing with tryptase level and allergy panels were not performed, as these are outpatient tests.

Discussion

Acute local reactions to COVID-19 vaccine consisting of mostly pain at the injection site are the most frequently reported adverse reactions among vaccine recipients. Recipients younger than 64 years old reported local reactions more frequently than those older than 65 years old. The second most frequently reported local reaction was axillary swelling or tenderness. Lymphadenopathy of the arm and neck occurred in 1.1% of vaccine recipients and 0.6% for placebo. Symptoms occurred within 2–4 days after vaccination and lasted for a duration of 1–2 days. During the trials, it was reported that three vaccine recipients were diagnosed with Bell's palsy while only one was in the placebo group.[12]

Monitoring of the Moderna COVID-19 vaccine has found 10 cases of anaphylaxis after the administration of 4,041,396 first doses of the Moderna COVID-19 vaccine. In 9 out of these 10 cases of anaphylaxis, the recipient of the vaccine had onset of symptoms within 30 min of administration. In addition, 9 of the 10 anaphylaxis patients also have a history of allergic reactions, some even with a past case of anaphylaxis. All 10 of the reported anaphylaxis cases occurred in women. A report produced by the Vaccine Adverse Event Reporting System (VAERS) found that 80% of anaphylaxis cases reported occurred in women. This high percentage could be due to the fact that more women than men received the Moderna COVID-19 vaccine during the analysis period (61% of doses administered versus 36%). There was a similar VAERS analysis performed of the Pfizer-BioNTech® COVID-19 vaccine with two thirds of the first doses being administered to women. The anaphylaxis reports from both vaccines, Moderna and Pfizer-BioNTech, show similar characteristics in their anaphylaxis cases in that symptoms began soon after vaccination occurred, a strong female predominance and the patient experiencing anaphylaxis having a history of allergic reactions.[13]

The American College of Allergy, Asthma and Immunology (ACAAI) COVID-19 Vaccine Task Force recommends the following guidance in relation to risk of an anaphylaxis reaction due to vaccination. Anyone receiving the vaccine should be screened to determine possible risk of an allergic reaction to the mRNA COVID-19 vaccine. If a patient has ever had a severe allergic reaction to a vaccine in their past, then they should be referred to an allergist or immunologist regarding their COVID-19 vaccine. Also, if a patient has a severe allergic reaction within 4 h of their first dose of the Moderna or Pfizer-BioNTech, they should not get the second dose. The COVID-19 vaccine should always be administered in a health care setting, and recipients should be observed for 15–30 min post-vaccination to be monitored for any reactions. Most anaphylactic reactions have occurred within the first 15 min after injection. The Moderna or Pfizer-BioNTech vaccines should not be given to individuals who have a known history of allergic reaction to any component of the vaccine. The specific vaccine component has not been identified yet; however, PEG is one of the ingredients in the mRNA vaccines that is known to cause anaphylaxis.[14] PEG is an ingredient in many drugs but having allergies to it is rare because hypersensitivity to it depends on its molecular weight. However, those who are allergic will have severe or even fatal reaction.[15]

Due to increased public concern about general allergic reactions in relation to the Moderna and Pfizer-BioNTech COVID-19 vaccine, the National Institute of Allergy and Infectious Diseases (NIAID) is conducting a clinical trial called the Systemic Allergic Reactions to SARS-CoV-2 Vaccination. The purpose of this trial is to determine whether people who have severe allergies are at an increased risk to anaphylaxis after being administered the Moderna and Pfizer-BioNTech COVID-19 vaccines.[16]

As of this writing, the CDC recommends that patients who have had an anaphylactic reaction

to a COVID-19 mRNA should not receive additional doses of any mRNA COVID-19 vaccine.[16]

Interestingly, a study in Denmark notes that a second COVID-19 vaccine is actually safe after an initial anaphylactic reaction to a COVID-19 vaccine. Their study was conducted from January to April 2021, and included 61 patients who met criteria according to the Brighton Criteria for anaphylaxis.[17] No patients reported a prior history of allergic reactions to vaccines. Six of the 61 had received the Moderna vaccine. Four of them were re-vaccinated without any adverse event. The authors concluded that after proper diagnostic work up, it is safe to revaccinate the vast majority of patients with an adverse event to a COVID-19 vaccine, as most patients with an immediate adverse reaction did not have true allergic reactions.

Conclusion

Anaphylactic reactions to the COVID-19 vaccine are a rare occurrence. Local interim guidance cautions against giving a second dose when such a reaction has occurred. However, there are data to suggest that these may not be true allergy-mediated reactions, and thus it could be safe to get a subsequent vaccine dose. This topic remains of utmost importance, as widespread vaccination would help to quell the current COVID-19 pandemic.

Acknowledgements

This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

Author contributions

JM and JR saw this patient in the emergency department. LG and SB drafted the manuscript and performed the literature review. JM edited the manuscript and all authors approved the final manuscript.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Consent for publication

The patient provided written informed consent to publish the details contained within this case report.

Ethical board that approved the study

HCA Centralized Algorithms for Research Rules on IRB Exemptions (CARRIE)/ IRB manager issued approval (STUDY NUMBER 2021-039). Based on the information provided and attested as true, the research plan described does not require IRB oversight. This is because, the investigator is either (a) not engaging in research with human subjects as defined by federal regulations; (b) engaging in research with human subjects deemed excluded from IRB oversight per 45CFR46.102(l) OR (c) engaging in research with sufficient human subject protections in the design to meet one or more IRB exemption criteria set forth in 45CFR46.104.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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