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CASE REPORT

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A case with recurrent idiopathic anaphylaxis episodes starting soon after COVID-19 mRNA vaccination

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Abstract
Introduction: A patient was presented with a history of idiopathic recurrent anaphylaxis after administration of Pfizer BioNTech mRNA vaccine, and the attacks were controlled with omalizumab. To our knowledge, this is the first reported case of recurrent idiopathic anaphylaxis (IA) after administration of Pfizer BioNTech mRNA vaccine.
Case presentation: A 52-year-old man with recurrent episodes of IA after COVID-19 vaccination presented to our adult Allergy and Immunology Clinic. In the patient, urticaria and anaphylaxis episodes could not be controlled with high-dose antihistamine and systemic steroid treatment, and complete control was achieved with omalizumab treatment and anaphylaxis attacks completely regressed.
Conclusion: In cases of unexplained or recurrent anaphylaxis in adult patients, COVID-19 vaccination and timing should be questioned, and its association with anaphylaxis might be considered.

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a single-stranded RNA (ssRNA) virus. The COVID-19 disease emerged in Wuhan, China in December 2019 and caused a major pandemic all over the world. It is a mortal infection causing severe pneumonia, dyspnea, organ dysfunction, and even death, and therefore different vaccines have been produced under the emergency code.[1] Among the vaccines available under this emergency code, seven have been approved for emergency use by the World Health Organization (WHO). The BNT16b2 vaccine by Pfizer/BioNTech is among the vaccines that have received full approval under this code.[2] The company reported some local reactions such as redness, swelling, and pain at the injection site. In addition, many adverse events such as

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fever, headache, chills, vomiting, and generalized body pain have been reported. More serious adverse events such as appendicitis, hypersensitivity reactions, acute myocardial infarction, and cerebrovascular accidents have also been reported.[3]

Here, we present the first case of an adult with a history of recurrent idiopathic anaphylaxis (IA) after administration of Pfizer BioNTech mRNA vaccine.

Case Report

A 52-year-old male was referred to our adult Allergy Clinic for the management of recurrent anaphylaxis. He had no previous history of chronic diseases or allergic reactions and did not have a COVID-19 infection before receiving the COVID-19 vaccine. Urticaria attacks started 4 days after the first dose of Pfizer BioNTech SARS CoV-2 vaccination. He was admitted to various emergency departments for these urticaria attacks which were successfully treated with antihistamines in the emergency room (ER). The urticaria attacks recurred when antihistamines were not used. A second dose of Pfizer BioNTech SARS CoV-2 vaccine was administered approximately 2 months after the first dose. After this, urticaria attacks recurred almost daily.

The patient received the third dose of Pfizer BioNTech SARS CoV-2 vaccine approximately 1 month later. Four days after the third dose of vaccine administration, he experienced sudden onset of shortness of breath, drowsiness, swelling of the lips and throat, dizziness, and red rash on his body and was immediately transferred to the ER by ambulance.

In the ER, flushing, urticaria on the extremities and face, swelling of the tongue, lips, and uvula, hypotension, tachycardia, and dyspnea were detected. Intramuscular epinephrine and diphenhydramine were administered in the emergency department. The tryptase result obtained at the second hour of anaphylaxis episode was 8.17 ng/mL. The anaphylaxis was successfully treated in the emergency department, but urticaria and angioedema continued to occur every day, and anaphylaxis attacks recurred approximately once in a month. The patient was referred to our clinic by the emergency physician due to recurrent urticaria and/or angioedema and anaphylaxis attacks. On evaluation of the patient in the allergy clinic, it was learned that he had five anaphylaxis attacks and presented to the ER almost every day due to urticaria. No triggering factors or cofactors such as exercise or alcohol were detected in these attacks.

Serum tryptase levels measured 2 h and 1 day after anaphylaxis were 8.17 and 4.89 ng/mL, respectively. This difference was 2.30, more than 20% of the baseline value, verifying the anaphylaxis diagnosis. In addition, total IgE:100 IU/mL, anti-TPO:11.6 IU/mL, anti TG:17.7 IU/mL, C-reactive protein (CRP): 3 mg/L, and the other routine blood tests and stool examination regarding the parasitic infections were normal. Alpha-gal-specific IgE was negative. The patient was referred to the Hematology Department due to recurrent IA, and bone marrow biopsy was performed. c-KIT D816V mutation was negative in bone marrow biopsy. Skin tests for polyethylene glycol 3350 and polysorbate 80 were nonreactive. Abdominal ultrasonography did not reveal any lesion associated with hydatid cyst. A detailed cardiologic examination and elective angiography were performed, which revealed no cardiologic pathology. An epinephrine autoinjector was prescribed. Ten milligram cetirizine/day and 180 mg fexofenadine twice a day, and ketotifen 2 mg/day and methylprednisolone 16 mg/day were administered.

However, after the cessation of methylprednisolone, anaphylaxis attacks and chronic urticaria continued under high-dose antihistamines. Therefore, omalizumab 300 mg per month was initiated. On the second day of the first dose, urticaria or angioedema ceased. The patient was administered omalizumab 300 mg once a month on a regular basis. In the second month of his treatment, the use of high-dose second-generation antihistamines (4× regular dose) was reduced to two doses per day. Oral steroids were not needed. Ketotifen was discontinued. The patient, whose follow-up and treatment were continued in our Allergy and Immunology outpatient clinic, is now in the 11th month of omalizumab treatment. No urticaria, angioedema, or anaphylaxis attacks occurred since the day omalizumab treatment started.

Discussion

Anaphylaxis is a severe, potentially life-threatening, general or systemic hypersensitivity reaction, typically characterized by rapid onset and involvement of at least two different organs, usually the skin, and respiratory, cardiovascular, or gastrointestinal systems.[4,5] Idiopathic anaphylaxis is a form of anaphylaxis diagnosed when no trigger can be identified despite through clinical evaluation.[6]

Every patient with suspected anaphylaxis should be thoroughly evaluated. In cases similar to as in our patient, ambulance and ER records should be reviewed and acute serum tryptase measurements should be performed. These findings help physicians in the early recognition of anaphylaxis. Careful identification of triggers, cofactors, and comorbidities is essential. Idiopathic anaphylaxis is a multisystem disorder that may present with some symptoms such as urticaria, diarrhea, and angioedema. However, it is not always easy to diagnose anaphylaxis. Patients may have respiratory and/or cardiovascular compromise, which may present as cough, wheezing, shortness of breath, tachycardia, dizziness, and shock in severe cases, and it is important to make a differential diagnosis.[4,7] In particular, there is evidence that underlying cardiologic conditions increase the severity of anaphylaxis.[8,9] In our patient, a detailed cardiologic examination and elective angiography were performed, but no cardiologic pathology was found.

Vaccine-associated reactions are common with increasing vaccine administration.[10] COVID-19 vaccines are mostly based on new mRNA-based technologies, and many people are hesitant to be vaccinated due to the side effects.[11] Epidemiological data from studies have shown that allergic reactions to vaccines can occur with a frequency of 1 in 1,000,000 or up to 30 in 100,000 vaccinations.[12,13] In a study investigating the mechanisms of hypersensitivity reactions, it was reported that antigen presentation of water-soluble spike protein fragments as allergens may also activate allergen-specific B cells, which produces IgE antibodies and

triggers acute hypersensitivity reactions. The IgE–allergen complex binding with the receptor on mast cells triggers allergic mechanisms by causing the release of mediators such as histamine, prostaglandins, and leukotrienes.[14] In this report, we present a case of chronic urticaria with recurrent IA episodes after mRNA vaccine administration. It is not possible to explain it by the known allergic mechanisms. Previous studies have shown that SARS-CoV-2 infection is associated with elevated autoantibody reactivity[15,16] by the molecular mimicry mechanism specific to the SARS-CoV2 spike protein.[17] Also, it is well defined that chronic urticaria develops in autoimmune nature,[18] and some studies have reported that chronic urticaria can occur within a few months after mRNA vaccine injections.[19-21] However, any case with recurrence of IA after vaccination has not been reported until now. Randolph et al. reported recurrent IA in two patients with chronic urticaria positive to antithyroid antibodies, and the possible relation was pointed out.[22] We found the activation of masts cells in our patient in an anaphylaxis attack with an increase in tryptase levels, however, we could not indicate the triggering mechanism of mast cells. The antithyroid autoantibodies were also negative. We could not definitely exclude the development of autoantibodies since we could not measure them. Therefore, we may speculate that anaphylaxis can be triggered by the autoreactivity caused by mRNA vaccination as in chronic urticaria in this patient. Physicians should keep in mind that mRNA vaccination can be related to recurrent IA episodes. Thus, in patients with unexplained or recurrent anaphylaxis, COVID-19 vaccination and timing should be questioned, and its association with anaphylaxis might be considered. Although this case suggests a potential association between mRNA vaccine administration and recurrent IA, the causal relationship remains uncertain. Currently, there are no well-defined pathophysiological mechanisms linking mRNA vaccines with the onset of spontaneous anaphylaxis. In our case, it was revealed that the episodes were mast cell–mediated by the substantial increase in tryptase levels during an attack without a trigger. The relationship between mRNA vaccines and chronic urticaria is also mast cell–mediated. Although we could not identify the exact mechanism to explain the causality, we may speculate that the underlying mechanism of chronic urticaria triggered by mRNA vaccine may be responsible in this case, just being a more severe disorder. It is obvious that further studies are required to explore the potential immunological pathways involved.

The use of omalizumab in cases other than allergic asthma and chronic idiopathic urticaria is increasing.[23] In patients with mast cell disorders, omalizumab has successfully improved most symptoms, including anaphylaxis.[24] There are many case reports in the literature on the efficacy of omalizumab for the treatment of IA.[25-28] This case is unique in that the anaphylaxis attacks started after the administration of the Pfizer BioNTech mRNA vaccine and were controlled with omalizumab.

Conclusion

We presented a unique case of chronic urticaria with recurrent IA episodes initiated after BioNTech vaccination and treated successfully with omalizumab. On the occasion of this case, we would like to emphasize the fact that every anaphylaxis or suspected anaphylaxis should be referred to an allergist as soon as possible. Therefore, it is important that awareness of anaphylaxis and vaccine reactions is imparted through social or medical studies among both public and physicians.

Declaration of Patient Consent

The patient was informed that his data would be shared in the case report, and written consent was obtained from him.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

AI Declaration

No artificial intelligence (AI) tools or systems were used in the development, writing, analysis, or any other aspect of this manuscript.

Authors' Contributions

PK, SD, DEK, DU, and AG have made substantial contributions to conception and design; has been involved in drafting the manuscript or revising it critically for important intellectual content. All authors read and approved the final manuscript.

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