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CASE REPORT

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# Delayed Urticaria- Angioedema After mRNA Vaccine in an Adolescent Patient: Case Report

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## ABSTRACT

Messenger RNA (mRNA) vaccines have long been suggested as encouraging candidates for widespread vaccination since they are manufactured rapidly and induce both humoral and cellular immune system components against pathogens. Available data on the efficacy and safety of these vaccines are relatively limited and the spectrum of skin reactions is still unclear. We would like to contribute to the literature by presenting a rare case with cutaneous reactions and discussing the skin complications of these kinds of vaccines. Our patient was a 17-year-old healthy female patient who applied to the pediatric emergency department with urticarial plaques that started from the legs and spread to the trunk nearly 80 hours after the second dose of the BioNTech-Pfizer COVID-19 vaccine was applied. The patient, whose skin lesions recurred more severely within 24 hours at home, and who noticed mild swelling in the fingers of the right hand and on the lip, was brought to the emergency service for the second time. Patients and physicians should be aware of the risk of delayed adverse skin reactions as well as the development of immediate hypersensitivity reactions such as urticaria and angioedema after administration of an mRNA COVID-19 vaccine.

**Keywords:** mRNA vaccine, COVID-19, Urticaria, Angioedema

## INTRODUCTION

Messenger RNA (mRNA) vaccines have long been assumed as promising candidates for widespread vaccination as they are fast and simply produced and stimulate both humoral as well as cellular protection against viral antigens. This is the first time that these kinds of vaccines are utilized in humans. Recently, the FDA granted emergency approval to the Pfizer-BioNTech COVID-19 vaccine on November 12, 2020 and approved it on August 23, 2021. mRNA vaccines imitate the natural infection with the virus, keeping only a short synthetic viral mRNA that encrypts the necessary antigen, the spike protein of SARS-CoV-2 enveloped in lipid nanoparticles, thus infiltrating the cell membrane into the cytoplasm and generating spike protein for succeeding antigen presentation and immune system triggering. The existing data on the effectiveness and safety of these vaccines are comparatively limited, and the spectrum of cutaneous reactions is still uncertain (1,2).

We would like to contribute to the literature with our experience of a rare case having delayed cutaneous complications, and comment on the cutaneous complications of mRNA COVID-19 vaccines.

## CASE REPORT

Our patient was a 17-year-old female patient with no pre-existing disease who was admitted to the pediatric emergency department due to urticarial plaques starting from the legs and spreading to the trunk, which occurred approximately 80 hours after the second dose of the BioNTech-Pfizer COVID-19 vaccine (Figure 1). The patient had no triggering factors (signs of infection, unknown food

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intake, plant-animal allergen exposure, etc.) No reaction was observed after the first dose of the COVID-19 mRNA vaccine. The patient, who had diffuse urticarial lesions, was administered 1 mg/kg methylprednisolone parenterally in the emergency department and was discharged home after being prescribed an antihistamine. The patient's history and family history were unremarkable. The patient, whose lesions recurred more severely within 24 hours at home, and who noticed mild swelling in the middle and 4th fingers of his right hand (Figure 2) and lip, was admitted to the emergency service for the second time. 1 mg/kg/day methylprednisolone and 2 mg/kg/day pheniramine were started. In the physical examinations of the patient, PCR swab and acute phase reactants (CRP, procalcitonin, sedimentation rate) were negative for SARS-CoV-2 infection, there was nothing significant in the complete urinalysis, and no growth was detected in the urine culture. Parasites and eggs were not seen in the stool. The total IgE level of the patient who did not have eosinophilia in the complete blood count was 611 IU/ml. The skin prick test, which was performed according to her age and included some indoor and outdoor aeroallergens, was negative. We did not perform a skin test for the vaccine since the mechanism of delayed cutaneous reactions has been presently unidentified. The lesions of the patient, who responded to the current treatment from the second day of hospitalization, faded and did not recur. The patient was discharged after home treatment was arranged.

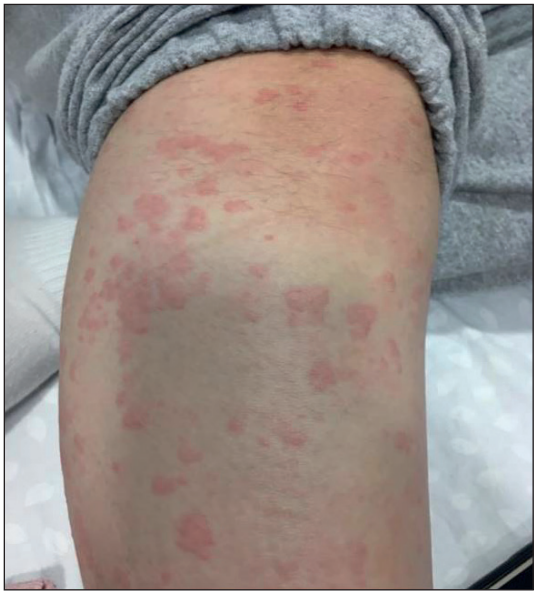

**Figure 1.** Urticarial lesions are seen over the upper surface of the right leg.

## DISCUSSION

The mechanism of both immediate and delayed allergic reactions is presently unidentified, although active and inactive vaccine ingredients, *e.g.,* polyethylene glycol (PEG), have been anticipated as potential offender allergens (3). Immediate (type I) hypersensitivity reactions develop within less than 4- 6 hours after vaccination and are mediated through IgE-dependent mediator release. Type I reactions may range from mild, with urticaria-angioedema only, to life-threatening with anaphylactic shock**.** In the case of COVID-19 vaccines, PEGs and cross-reactive polysorbate 80 have been held responsible to be the triggering factors for immediate reactions (4). An alternative explanation for the development of delayed cutaneous reactions may be the result of delayed T-cell responses to vaccine components or their excipients. The true incidence of type I and delayed reactions is not well-known.

In a study, 4.775 subjects underwent BNT162b2 mRNA vaccination, and two cases (2/4775; 0.04%) of vaccine-related urticaria were detected, lasting less than a week and responding to oral antihistamines (5). In a series of 6 patients, localized and generalized urticarial allergic dermatitis secondary to Moderna SARS-CoV-2 vaccination were described (6). In the international registry of the American Academy of Dermatology and the International League of Dermatological Societies, urticaria (n:16 first dose and n:7 second dose of the Moderna vaccine: 23/343; n:9 first dose and n:8 second dose of the Pfizer vaccine: 17/71), was noted among 414 patients with

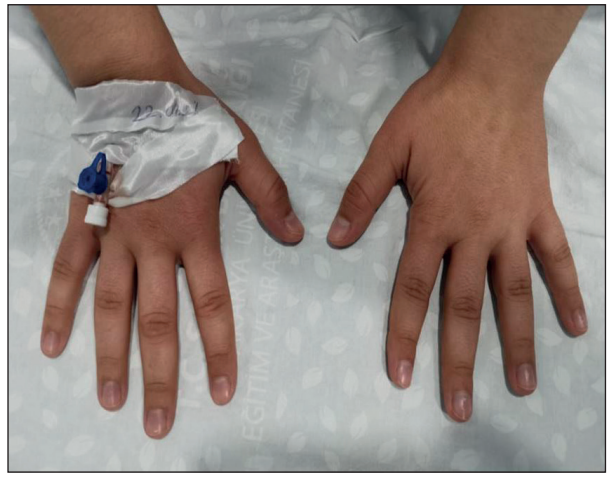

**Figure 2.** Mild edema is observed in the middle (3rd) and ring (4th) fingers of our patient's right hand.

cutaneous adverse events due to SARS-CoV-2 vaccination (7). The most common reaction was urticaria followed by other rashes, i.e., morbilliform, pityriasis-form, bullous drug eruption, fixed drug eruption, etc. (8-10).

Anaphylaxis to the first dose may be a contraindication to succeeding mRNA vaccination; however, various mild or nonimmediate allergic reactions are not (11). Acute urticaria alone after any mRNA or CoronaVac vaccination should not be seen as a contraindication for revaccination (12). Type I allergic reaction after dose 1 of the mRNA vaccine may contribute to unfinished vaccination. Allergists should be prepared to guide these kinds of subjects to preclude partial vaccination.

The conditions for allergy testing before vaccination are severe type I allergic reaction (e.g., urticaria, angioedema, anaphylaxis) to the first vaccine dose and/or to constituents of the vaccine, and a known history of allergy to PEG and polysorbate. There is no uniform diagnostic testing for suspected hypersensitivity to PEGs. Cross-reactions to polysorbate 80 must also be kept in mind (**2**). In cases with positive tests, other non-mRNA vaccines may be utilized in these individuals, if accessible and not contraindicated for other reasons (4).

Delayed cutaneous reactions have previously been reported by many groups as rather large local reactions. Delayed urticaria reactions to mRNA-type COVID-19 vaccines have not been reported often before. "Delayed urticaria" is acute urticaria but it happens later by possibly different immunologic mechanisms than the usual ones classified as immediate hypersensitivity reactions. One of the earliest reports detailing cutaneous allergic reactions to mRNA COVID-19 vaccines is by McMahon et al. In this study, in which 414 cutaneous adverse reactions were reported, urticaria occurred in 23 subjects, 18 of whom were >24 hours post-vaccination after Moderna mRNA COVID-19 vaccination. After Pfizer-BioNTech mRNA COVID-19 vaccination, 17 subjects developed urticaria in total and it occurred 24 hours later in 16 subjects (13). Pitlick et al. also reported the development of delayed systemic urticaria rash (>4 hours after vaccination) after a single dose of mRNA COVID-19 vaccine in 12 patients from 2 different medical centers (3).

Three different cases of angioedema occurring within days of administration of an mRNA COVID-19 vaccine severe enough to warrant an emergency room visit were reported by Watts et al. No elements were identified that could predict the development (or severity) of angioedema in each case in the clinical history of patients. Fortunately, all patients were successfully treated and none died. Patients with delayed angioedema of this type have rarely been reported, and remarkably, case 2 took the second dose of the vaccine without recurrence of cutaneous manifestations or delayed angioedema (14).

In conclusion; patients and clinicians should be cognizant of the risk of adverse cutaneous reactions, containing the possibility of delayed as much as immediate reactions such as urticaria and angioedema after administration of a novel mRNA COVID-19 vaccine. The benefits of receiving the COVID-19 vaccine continue to outweigh the risk of a potential adverse reaction occurring, for most individuals.

**Authorship Contributions**

Concept: **Öner Özdemir, Ümmügülsüm Dikici, Olena Erkun,** Design: **Öner Özdemir, Ümmügülsüm Dikici, Olena Erkun,** Data collection or processing: **Ümmügülsüm Dikici, Olena Erkun,** Analysis or Interpretation: **Öner Özdemir, Ümmügülsüm Dikici,** Literature search: **Ümmügülsüm Dikici, Olena Erkun,** Writing: **Öner Özdemir, Ümmügülsüm Dikici, Olena Erkun,** Approval: **Öner Özdemir, Ümmügülsüm Dikici, Olena Erkun.**

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