

## Hypothesis & Experience

### Case Report



# Delayed urticaria after BNT162b2 booster vaccination at previous intradermal test site with severe acute respiratory syndrome-coronavirus-2 spike protein

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## ABSTRACT

Urticaria is a common cutaneous adverse event from coronavirus disease 2019 vaccination. Previous studies hypothesized that excipients as polyethylene glycol in BNT162b2 vaccine and polysorbate in ChAdOx1 nCoV-19 vaccine are allergens. A 28-year-old woman had urticaria after a booster vaccination with BNT162b2 at the site of previous intradermal injection with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) spike protein. This reaction emphasized that delayed urticaria may not be an allergic reaction to excipient but rather to the immunogen as such as SARS-CoV-2 spike protein.

**Keywords:** Delayed urticaria; COVID-19 vaccination; BNT162 vaccine; Pfizer

## INTRODUCTION

Urticaria is a common cutaneous adverse event from coronavirus disease 2019 (COVID-19) vaccination. The onset is delay (>4 hours) in most reaction [1]. The exact immunological mechanism is yet to be identified. We herein report a case of localized urticaria after a booster vaccination with BNT162b2 (Pfizer Inc.; Philadelphia, PA, USA) at the site of previous intradermal injection with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) spike protein. This case might shed some light on the pathomechanism of urticaria induced by COVID-19 vaccination. This case report was approved by the Institutional Review Board (IRB) of Faculty of Medicine, Chulalongkorn University (IRB number: 668/64).

**Conflict of Interest**

The authors have no financial conflicts of interest.

**Author Contributions**

Conceptualization: Pawinee Rerknimitr. Formal analysis: Jidapa Triwatcharikorn. Investigation: Jidapa Triwatcharikorn. Methodology: Jidapa Triwatcharikorn. Project administration: Pawinee Rerknimitr. Writing - original draft: Jidapa Triwatcharikorn. Writing - review & editing: Pawinee Rerknimitr, Jettanong Klaewsongkram.



**Fig. 1.** An indurated erythematous papule after 12 hours of intradermal test with 1/100 and 1/1000 severe acute respiratory syndrome-coronavirus-2 spike protein dilution at volar side of left forearm.



**Fig. 2.** An urticarial reaction occurred 36 hours after an injection of booster dose BNT162b2 COVID vaccine.

**CASE REPORT**

A 28-year-old woman was a healthcare volunteer to identify nonirritating concentration of SARS-CoV-2 spike protein for skin intradermal testing (IDT). The IDT was undertaken with 1/100 and 1/1,000 synthetic SARS-CoV-2 spike peptides (Mimotopes Pty Ltd., Mulgrave, VIC, Australia) dilution at volar side of left forearm. After a 30-minute observational period, the skin test showed negative result. However, 12 hours later, a 1-cm infiltrated erythematous papule appeared at the 1/100 spike protein injection site (**Fig. 1**) and disappeared spontaneously 3 days later. The volunteer had completed CoronaVac (Sinovac, Beijing, China) vaccination 3 weeks earlier and had no prior COVID-19 infection. Four weeks after the skin testing, BNT162b2 was given as a booster vaccine. Thirty-six hours after the injection, an itchy indurated wheal occurred on the previous IDT-positive test site (**Fig. 2**). The 0.1% betamethasone valerate cream was applied and the lesion faded in 2 hours. She had fever, myalgia, and headache. Systemic symptoms resolved after 3 days. Physical examination showed an indurated erythematous papule, 1 cm in diameter on volar side of left forearm.

## DISCUSSION

Though IDT is mainly used for type 1 IgE-mediated drug hypersensitivity reaction (DHR), delayed reading can serve as a tool for non-immediate DHR testing [2]. The volunteer showed a reaction from spike protein at 12-hour period, therefore this reaction may not be IgE-mediated in nature. The similar pattern of reaction has been reported to occur from IDT with COVID-19 vaccines in individuals who have already been vaccinated. It is thought to be a sign of desired cellular immune protection as the second exposure to a specific allergen, sensitized T cells mount immune responses resulting in inflammation [3].

Interestingly, delayed urticaria developed at the site of IDT with spike protein after BNT162b2 was given. A recent study has demonstrated the presence of SARS-CoV/SARS-CoV-2 spike protein in endothelial cells in urticarial rash from a COVID-19 patient by Immunohistochemistry study [4]. Moreover, we have seen cases of COVID-19 vaccine-associated urticaria who were tested positive with spike protein IDT. The fact that urticaria appeared at the site of spike protein injection is intriguing. Patients who recovered from COVID-19 infection can continue to have SARS-CoV-2 RNA detected in their upper respiratory tract specimens for up to 12 weeks after symptom onset [5, 6]. Though there are no studies to investigate how long SARS-CoV-2 RNA/spike protein remain in skin after the infection, we consider that the spike protein that was introduced through the skin may remain at the test site until the time of the booster vaccine is given (4 weeks later). Once the booster vaccine is administered, it is capable of eliciting innate and adaptive immunity to SARS-CoV-2 [7]. Plethora of immune cells are activated and may lead to a reaction with the residual spike protein inducing urticarial lesion. Unfortunately, skin biopsy was not obtained from the subject due to the ethical consideration. The delayed localized urticaria occurred solitary at the previous skin tested site. According to the fact that CoronaVac and BNT162b2 do not share any same excipients, and the synthetic SARS-CoV-2 spike peptides were diluted with normal saline (without added excipients), this delayed localized urticaria should be the reaction between embedded SARS-CoV-2 spike peptides and host immune responses.

Urticaria is frequently IgE-mediated, however, mast cell degranulation can be induced via activation of complement systems, IgG, cytokines, chemokines, and other inflammatory mediators [8, 9]. Delayed urticaria (onset > 24 hours) can be associated with COVID-19 as well as other vaccines [10, 11]. The pathophysiology of this reaction is not well understood. With findings from the previous reports together with this present case, we hypothesize that delayed urticaria from COVID-19 vaccines is non-IgE-mediated immune reaction, not to the vaccine excipients but rather to SARS-CoV-2 spike protein. This is evident by the fact that those with delayed urticaria from the first dose can be safely vaccinated in the second dose without fatal recurrence [1].

In conclusion, a 28-year-old woman who had completed CoronaVac vaccination 3 weeks earlier underwent intradermal test with 1/100 and 1/1,000 synthetic SARS-CoV-2 spike peptides. A delayed localized urticaria occurred at the test site after she received BNT162b2 booster vaccination. Delayed urticaria from COVID-19 vaccination may not be an allergic reaction to the excipients but rather to the immunogen such as SARS-CoV-2 spike protein.

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