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Delayed local reactions after the first administration of the ChAdOx1 nCoV-19 vaccine

To the Editor,

Amid the COVID-19 pandemic, novel SARS-CoV-2 vaccines are expected to be the key to overcome this global health crisis. Since vaccination was initiated in December 2020, real-world data regarding adverse reactions and tolerability remain limited.[1] Herein, we report four cases of delayed local reaction that first occurred more than 1 week after ChAdOx1 nCoV-19 [AZD1222] (AstraZeneca/Oxford) vaccination among 7282 healthcare workers (HCWs) (4/7282, 0.05%) in a tertiary hospital. The Institutional Review Board of Asan Medical Center approved the study (2021–0323) and all subjects provided informed consent. Table 1 summarizes the demographic and clinical characteristics of the patients, who were all females and aged 30–48 years. Two patients had a co-existing allergic skin disease (solar urticaria or chronic idiopathic urticaria), and one had a history of delayed hypersensitivity reaction to antibacterial ophthalmic ointment containing polysorbate 20. However, none of them had previously experienced adverse reactions to any vaccine. The morphology and clinical course were heterogeneous across the cases (Figure 1). Patients 1 and 2 reported mild delayed local reactions and experienced mild or no solicited symptoms. Topical steroids or non-steroidal anti-inflammatory drugs (NSAIDs) were prescribed according to co-existing symptoms. Meanwhile, Patients 3 and 4 had more severe local reactions. The skin lesion was both tender and warm. They underwent laboratory tests for complete blood count, chemistry panel, erythrocyte sedimentation rate, and C-reactive protein, but all of these tests obtained normal results. Systemic corticosteroids and NSAIDs were prescribed. Patients with more severe delayed local reactions tended to experience more intense solicited systemic symptoms. Patient 3, who presented the most severe local reaction, suffered from extensive myalgia and arthralgia limiting daily activities following the first administration. Intriguingly, in all cases, the skin lesion started to

TABLE 1 Summarized cases of delayed local reactions after the first administration of ChAdOx1 nCoV-19 vaccine.

	Patient 1 (42/F)	Patient 2 (30/F)	Patient 3 (47/F)	Patient 4 (48/F)
Allergic diseases	None	None	Solar urticaria	Chronic idiopathic urticaria
Previous drug adverse reactions	None	None	Delayed rash due to neomycin ophthalmic ointment	None
Onset (days since vaccination)	9	11	9	16
Overall duration	5	2	7	3
Treatment	Topical steroid	NSAIDs, ice pack application	Systemic steroids, NSAIDs	Systemic steroids, NSAIDs, topical steroids
Symptoms preceding delayed local reaction (duration of symptoms)	Fever, headache (2 d)	None	Fever, chill, myalgia, arthralgia (4 d)	Fatigue, globus pharyngeus (10 d)
Symptoms coexisting with local reaction	Pruritus	Pain	Pain, pruritus, warm sensation	Pain, pruritus, warm sensation

Abbreviation: NSAIDs, Nonsteroidal anti-inflammatory drugs.

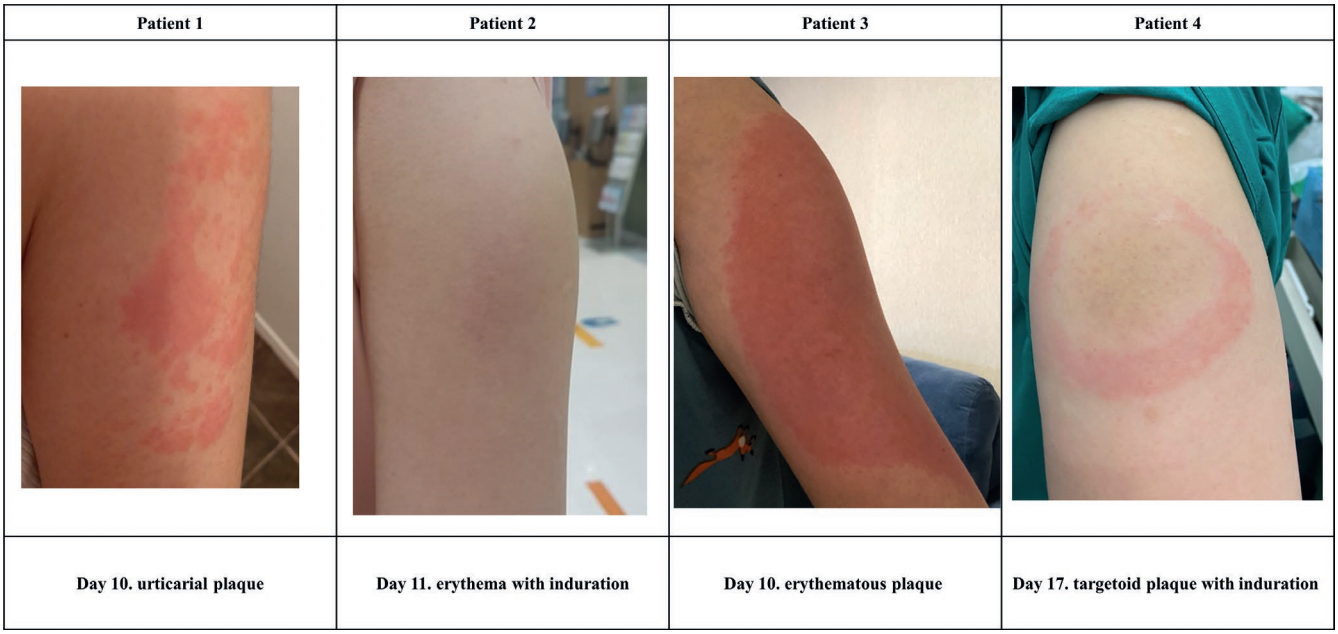

FIGURE 1 Delayed local reactions after the first administration of ChAdOx1 nCoV-19 vaccine, Images of skin lesions and their descriptions in each case

develop after the complete resolution of systemic symptoms. This temporal discordance was one of the main reasons that made patients feel embarrassed and worried about unexpected prolonged-adverse reactions.

The vaccine's local side effects are common, reflecting a normal immune response. They usually last for several days and subside spontaneously.[2] In the phase 2/3 trial of the ChAdOx1 vaccine, the most common local adverse reactions included pain and tenderness on the injection site.[3] However, the data only covered up to 7 days after vaccination. Meanwhile, in the phase 3 trial of the mRNA-1273 vaccine, 0.8% of the patients had delayed injection-site reactions (those with onset on or after day 8).[4] Blumenthal et al also reported 12 cases of delayed local reactions, which initially occurred 4–11 days after mRNA-1273 vaccination.[5] The pivotal clinical trial of the BNT162b2 vaccine did not address delayed local reactions.[6] Among the 343 HCWs injected with the BNT162b2 vaccine in our center, which were almost 20 times less than those administered the ChAdOx1 vaccine, none reported delayed local reactions.

All cases were occurred in relatively young women. Patients with the history of allergic skin disease or drug hypersensitivity experienced more severe delayed local reactions compared to those without such histories. However, currently, it is difficult to determine the risk factors for delayed local reaction due to the limited number of cases and the lack of a clear mechanism. More accumulation of cases providing information regarding the patient's allergic status including total or specific IgE, skin test results to vaccine components, and autoimmunity related to chronic urticaria may help to identify potential risk factors for delayed reaction and the possible pathophysiology.

Although active antigen stimulates local reactions, other protein ingredients or excipients of vaccine may also induce delayed reactions

resulting from hypersensitivity. However, there is no feasible way to discern the type of immunologic pathway or causative agent.[2] If the cases are T-cell-mediated reactions against the SARS-CoV-2 spike glycoprotein, it is unclear if the magnitude of local reaction is related to systemic reaction in the context of infection. The morbilliform rash reported both as an adverse reaction of the BNT162b2 vaccine and as a manifestation of COVID-19 infection suggest the spike protein as a shared trigger of immune reactions.[7] The recurrence of a similar reaction after the second dose also needs to be carefully monitored. Among the mRNA-1273-related large local reactions, the recurrence rate was 50% and half of them were less severe than the initial reactions.[5]

Considering the rarity and long time-to-onset (more than a week) interval of delayed local reaction, it might be regarded as irrelevant to vaccination or diagnosed as cellulitis, leading to unnecessary antibiotic treatment. This report might be the first to describe delayed local reaction resulting from ChAdOx1 nCoV-19 vaccination. Given the speed of mass vaccination, clinicians need to be aware of potential adverse reactions and prepared to provide appropriate management.

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In search of the golden ratio for cannabis allergy: Utility of specific allergen-to-total IgE ratios

To the Editor,

The most important "diagnostic test" for CA is a detailed history. However, a positive history is no absolute proof of CA, mainly because of physiological effects of cannabis, that is, (rhino)conjunctivitis presence and possibly because of incorrect interpretation or recollection of symptoms by the patients under the drug's influence.

Abbreviations: CA, cannabis allergy; CCDs, cross-reactive carbohydrate determinants; CI, confidence interval; CSA, cannabis sativa allergic patients; nsLTPs, nonspecific lipid transfer proteins; P+LTP-, controls sensitized to pollen without nsLTP sensitization; P+LTP+, controls sensitized to pollen and nsLTPs; r, recombinant; sIgE, specific immunoglobulin E; ST, skin tests; tIgE, total immunoglobulin E.