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Article type : Letter to the Editor

Delayed cutaneous reaction to ChAdOx1 nCoV-19 vaccine: Is it an ‘AstraZeneca arm’?

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/JDV.17476](#)

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Keywords: delayed cutaneous reaction, ChAdOx1 nCoV-19 vaccine

Words count: 487

Number of Table: 1

Number of Figure: 1

References: 7

Funding source: None

IRB approval: Yes (Number HYUH 2021-03-052)

Disclosure of potential conflict of interest:

Jeong Eun Kim declare to have no conflict of interest.

Hyun Lee declare to have no conflict of interest.

Seung Sam Paik declare to have no conflict of interest.

Ji-Yong Moon declare to have no conflict of interest.

Ho Joo Yoon declare to have no conflict of interest.

Sang-Heon Kim declare to have no conflict of interest.

Acknowledgments: The patients in this manuscript have given written informed consent to publication of their case details

Dear Editor:

Blumenthal et al.¹ reported cases of delayed large local reaction to the mRNA-1273 Moderna COVID-19 vaccine, which was called the ‘Moderna arm’ for the first time. Intriguingly, this phenomenon was observed primarily in Moderna vaccine, but rarely reported in BNT162b2 COVID-19 vaccine by Pfizer-BioNTech.²⁻⁴ Because the reports were limited to mRNA vaccines, a delayed type hypersensitivity reaction to the excipient polyethylene glycol (PEG) in both mRNA vaccines was suggested as one potential etiology.^{4,5}

Unlike to these mRNA vaccines, ChAdOx1 nCoV-19 (AZD1222) is a replication-defective chimpanzee adenovirus-vectored vaccine and it includes polysorbate 80 as an excipient.⁶ Recently, we have observed delayed cutaneous reactions around the injection site of the ChAdOx1 nCoV-19 vaccine. We report four cases with such reactions that developed at least three days (range, Day 4 to 17) after the first dose of vaccination (Table 1). All the patients were female healthcare workers (1 physician, 2 nurses, and 1 laboratory technician) at our university hospitals and were ethnically Korean. They did not have a previous history of hypersensitivity reactions to drugs or any vaccine. Only one patient had allergic rhinitis but did not require regular medication. Routine blood tests including complete blood cell counts, C-reactive protein and serum IgE were unremarkable. All patients had a large delayed skin reaction that started with erythematous swelling (Figure 1a-d), and three developed systemic symptoms including fever, chill, and myalgia from the day of vaccination and that resolved before the delayed skin reactions. Thus, at the development of delayed local skin reactions, none of the patients experienced concurrent systemic symptoms. The delayed skin lesions resolved after short-term treatment, such as oral antihistamines or topical or oral corticosteroids, while the duration of skin reaction varied from 4 to 18 days. Skin biopsy from three patients showed superficial perivascular and perifollicular lymphocytic infiltration with sparse eosinophils (Fig. 1e-k). These findings suggest that the delayed local cutaneous reactions are mediated by hypersensitivity mechanisms. However, the exact pathophysiological mechanism remains unclear if they are true hypersensitivity reactions. One reason for this controversy is that the skin tests (patch, prick, and intradermal test) of the patient who was injected BNT162b2

vaccine were all negative.² In the aspect of hypersensitivity reaction, unlike PEG, polysorbate 80 in ChAdOx1 nCoV-19 vaccine has been used in other vaccines before, it is still unclear which antigen in the vaccine caused these reactions.

Our report suggests that the delayed local cutaneous reactions to the COVID-19 vaccines are not vaccine-specific, since both mRNA vaccine and viral-vector vaccine showed such reactions. Before implementing a mass vaccination campaign with various COVID-19 vaccines, clinicians should be aware of the possible 'COVID arm' to avoid unnecessary tests or treatment. While the Centers for Disease Control and Prevention reported that patients who experienced delayed cutaneous reactions to the first dose of COVID-19 vaccine could be safely vaccinated with the second dose,⁷ more data are required to understand and manage the 'COVID arm' to various COVID-19 vaccines.

Table1. Demographic and clinical data of subjects with delayed cutaneous reaction to ChAdOx1 nCoV-19 vaccine*

*None of the patients had known previous SARS-CoV-2 infection. The clinical data were reported by patients, and symptoms were evaluated by a dermatologist or allergist.

Figure Legends

Figure 1. Clinical photographs and the representative histopathologic findings of delayed cutaneous reactions to the ChAdOx1 nCoV-19 vaccine.

(a) Patient 1 presented considerable induration with pain and tenderness on Day 5. After 3 days of oral prednisolone 30 mg, the skin lesion resolved.

(b) Patient 2 started a painful erythematous swelling on Day 5. Without treatment, the skin lesion became larger (15 x 8 cm), but pain decreased, and pruritus occurred on Day 18. The skin lesion gradually improved after 3 days of oral antihistamine and topical corticosteroid.

(c) Patient 3 presented with erythematous tender plaque on day of 17. There was no immediate skin reaction after vaccination. On Day 18, the patient underwent skin biopsy and was prescribed oral antihistamine and topical corticosteroid. Four days later (on Day 22), the skin lesion was much improved.

(d) Patient 4 suffered from 18 x 10 cm sized itchy erythematous swollen plaque on Day 16. There was no immediate cutaneous symptom after vaccination and no concurrent systemic symptom.

(e-g) Skin biopsy specimen from patient 4 shows superficial perivascular and perifollicular lymphocytic infiltration and some eosinophils. Neutrophils are present inside dilated small vessels. Immunohistochemistry reveals mainly CD3+ T cells with sparse exocytosis (h) and few CD20+ B cells (i). There is a mixed population of CD4+ (j) and CD8+ (k) cells, but CD4+ is predominant. These findings are consistent with a delayed hypersensitivity reaction (e: H&E X40, f: H&E X200, g: H&E X 400, h: CD3 X40, i: CD20 X40, j: CD4 X40, k: CD8 X40).

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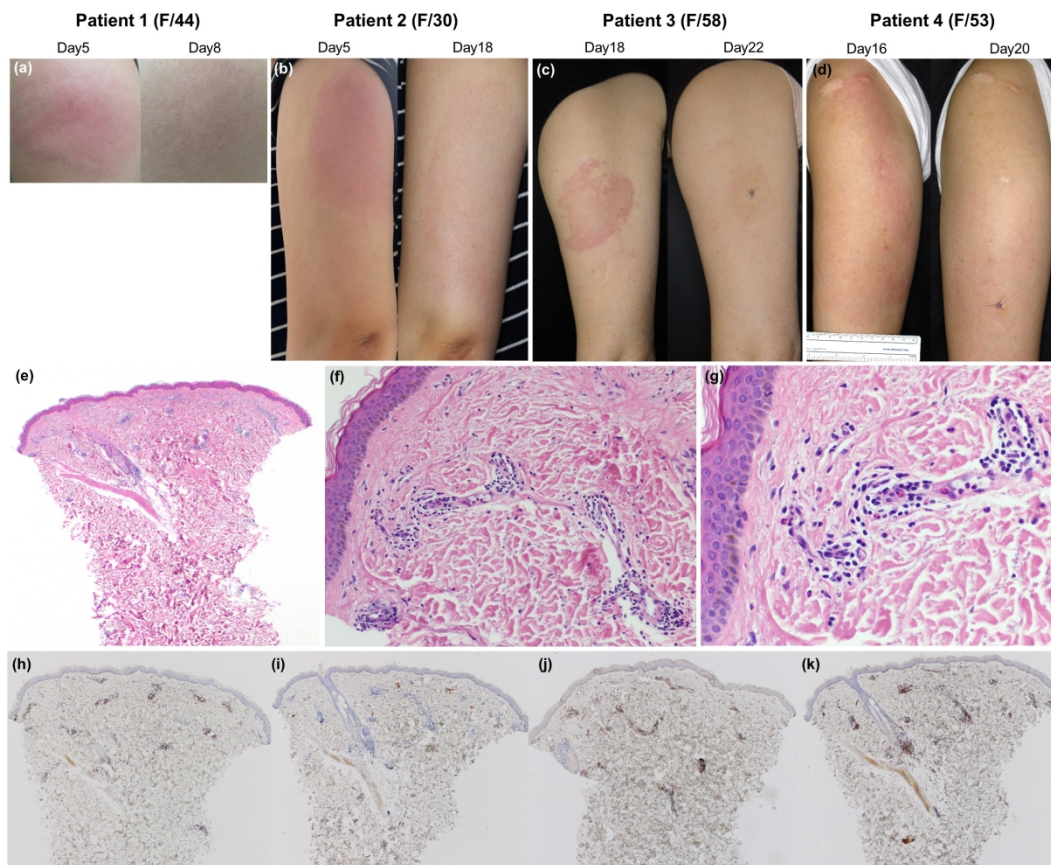
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Table1. Demographic and clinical data of subjects with delayed cutaneous reaction to ChAdOx1 nCoV-19 vaccine *

Patient	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	44	30	58	53
Sex	Female	Female	Female	Female
Past medical history	Allergic rhinitis	No	Dyslipidemia	Vitiligo
Current medication	No	No	Atorvastatin	No
Past history of cutaneous reaction to vaccination	No	No	No	No
Day of skin reaction onset after COVID-19 vaccination	4	5	17	14
Symptoms and signs of cutaneous reaction	Erythema, swelling, pain, tenderness	Erythema, swelling, pain, tenderness, pruritus	Erythema, swelling, pain, tenderness	Erythema, swelling, pruritus
Lesion size, cm	10 x 10	15 x 8	9 x 7.5	18 x 10
Immediate injection site reaction after vaccination	No	No	No	No
Immediate systemic symptoms after vaccination	Fever (38.5°C), chill, myalgia	Fever (38.4°C), chill, fatigue, headache	Fever (38.1°C), chill, fatigue, headache, myalgia	Fatigue, myalgia
Concurrent systemic symptoms with delayed skin reaction	No	No	No	No
Treatment	Oral prednisolone 30mg for 4 days	Oral antihistamine, topical corticosteroid for 3 days	Oral antihistamine, topical corticosteroid for 4 days	Oral antihistamine, topical corticosteroid for 4 days
Duration of skin reaction, days	4	17	7	6
Treatment response	Complete resolution	Complete resolution	Complete resolution	Complete resolution

*None of the patients had known previous SARS-CoV-2 infection. The clinical data were reported by patients, and symptoms were evaluated by a dermatologist or allergist.



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