A case of recurrent fixed drug eruption following the administration of 2 different coronavirus disease 2019 vaccines verified using intradermal and patch tests

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INTRODUCTION

Various dermatologic manifestations have been reported following coronavirus disease 2019 (COVID-19) vaccination, such as injection site local reaction, urticaria, morbilliform, papulovesicular, pityriasis, and vasculitis-like eruption.[1] However, fixed drug eruption (FDE) has been rarely reported: 2 cases vaccinated with BNT162b2 (Pfizer), 2 cases vaccinated with AZD1222 (AstraZeneca), and 1 case vaccinated with mRNA-1273 (Moderna).[2-6] Moreover, there has been no report of cases of FDE that developed after the administration of 2 different COVID-19 vaccines with regard to mix-and-match booster vaccinations. Herein, we report a case of recurrent FDE in a patient vaccinated with AZD1222 and mRNA-1273.

Abbreviations used:

FDE: fixed drug eruption
IDT: intradermal test
PEG: polyethylene glycol
PS80: polysorbate 80

CASE REPORT

A 50-year-old man presented with a 2-week history of pruritic, well-defined, purpuric-to-hyperpigmented annular patches with central blistering on the nape, trunk, both extremities, and penis (Fig 1, *A-C*). The lesions initially occurred 24 hours after the first dose of AZD1222 in March 2021 (Fig 1, *D*), then recurred 2 months later at the same sites 24 hours after the second dose of AZD1222 (Fig 1, *E*), and 8 months later, 24 hours after a booster dose of mRNA-1273. The patient denied concomitant symptoms, including fever and myalgia. His history of medications and allergic reactions to medications or vaccines was unremarkable. A punch biopsy of the blister area revealed confluent necrotic keratinocytes and eosinophilic infiltration of the epidermis (Fig 2, *A*). A biopsy from the patch area showed a hydropic change in the basal layer, pigment incontinence, and perivascular lymphohistiocytic mixed infiltration with eosinophils and melanophages in the upper-to-middermis (Fig 2, *B*). Diagnosed as FDE, the patient was treated with systemic and topical corticosteroids for 3 weeks. The lesions improved, leaving noted postinflammatory hyperpigmentation, and new lesions did not appear following corticosteroid tapering.

After 2 months, an intradermal test (IDT) was performed with 0.1% polysorbate 80 (PS80) and polyethylene glycol (PEG) on the dorsal aspect of the hand. After 48 hours, the IDT triggered erythematous patches on the lesional skin area with each material (Fig 3, *A* and *B*). Similarly, a patch test was performed with 1% PS80 and PEG on the lower portion of the back, which also showed a positive

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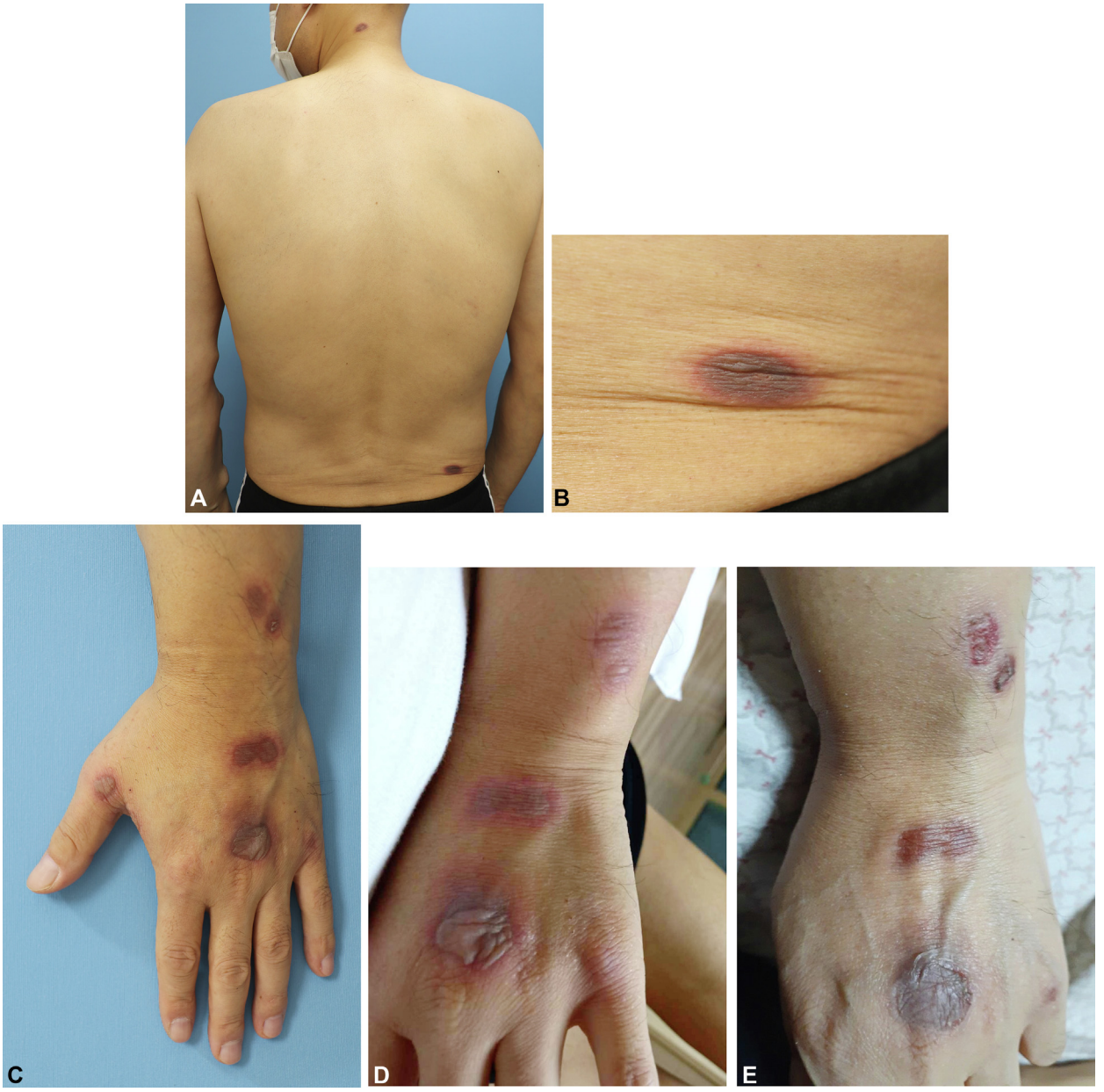

Fig 1. Clinical presentation of fixed drug eruption showing well-defined, purpuric-to-hyperpigmented annular patches with central blistering. The figure shows **(A)** the patient's back, **(B)** a closer view of the lower portion of the back, and **(C)** the patient's left hand following a booster dose of mRNA-1273. Similar lesions were photographed by the patient following the **(D)** first dose and **(E)** second dose of AZD1222.

reaction on the lesional skin area after 48 and 96 hours with each material (Fig 3, *C* and *D*). One week of washout period was maintained between each test, during which there was complete subsidence of the erythematous reaction. There was no reaction in the nonlesional skin area during each test. Unfortunately, the intradermal or patch test with AZD1222 or mRNA-1273 was unavailable because of the Korean government's regulations. The Naranjo Adverse Drug Reaction Probability Scale score was approximately 9, indicating a "definite" probability level. After consultation with the department of allergy and clinical immunology, any medication containing a large amount of PS80 or PEG, such as influenza vaccines and bowel preparation agents, was contraindicated in the patient.

DISCUSSION

Similar to previously reported cases of FDE, the time of its onset from vaccination was also 24 hours

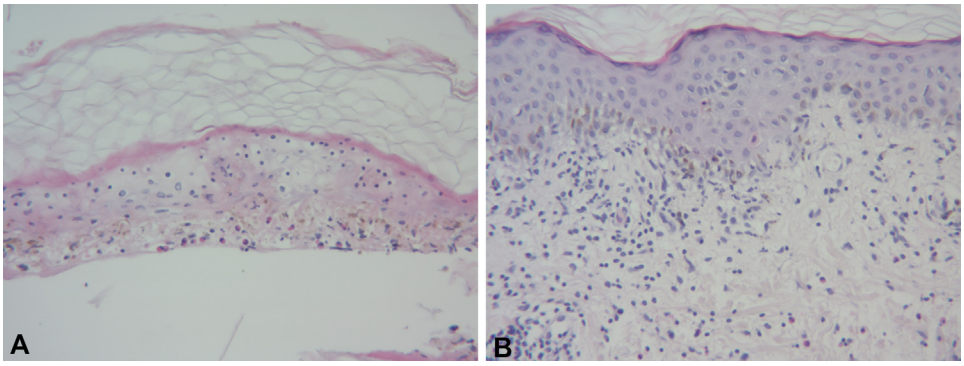

Fig 2. Histopathology. **A,** Punch biopsy of the blister area revealed detached epidermis with confluent necrotic keratinocytes and infiltration of mixed lymphocytes and eosinophils. **B,** Punch biopsy of the patch area revealed vacuolar degeneration of the basal layer, Civatte bodies, melanin incontinence, and perivascular lymphohistiocytic mixed infiltration of eosinophils and melanophages in the upper-to-middermis. (**A** and **B,** Hematoxylin-eosin stain; original magnifications: **A,** ×200; **B,** ×200.)

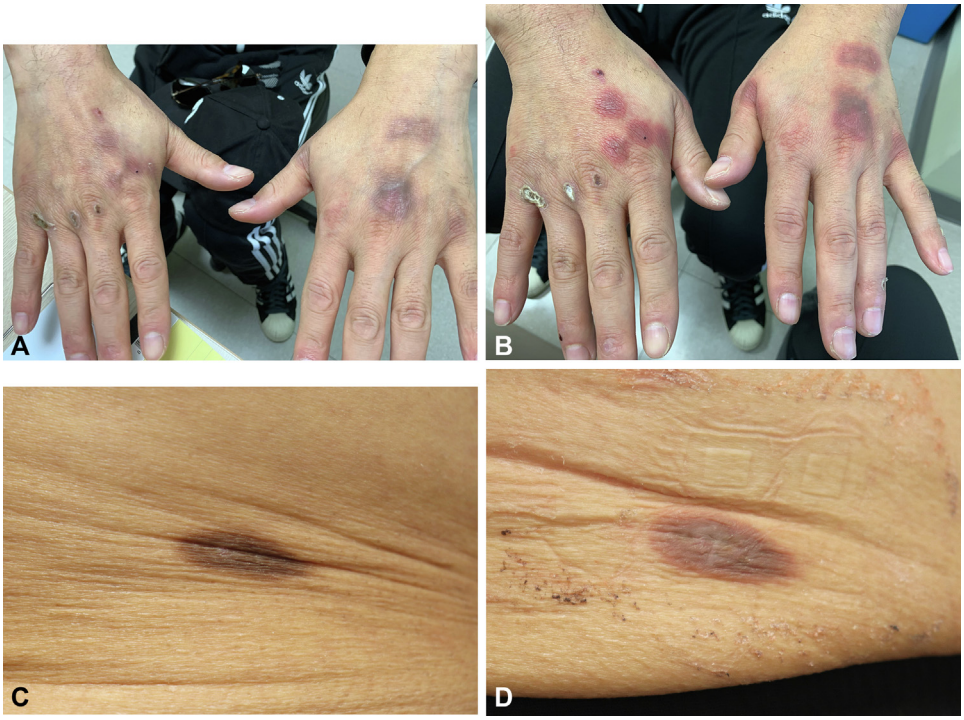

Fig 3. Provocation test results. An intradermal test with 0.1% polysorbate 80 and polyethylene glycol triggered a positive reaction on the lesional skin **(A)** before and **(B)** after a intradermal test on the dorsal aspect of the hand. A patch test with 1% polysorbate 80 and polyethylene glycol showed a positive reaction on the lesional skin **(C)** before and **(D)** after a patch test on the lower portion of the back.

in this case (Table I).[2-6] The patient showed a relatively wider distribution of lesions, involving the genital mucosa, than other cases. Uniquely, in this case, both the patch test and late-reading IDT yielded positive results for PS80 and PEG, indicating a type Ⅳ hypersensitivity reaction.

PS80 is a potential AZD1222 allergenic excipient, whereas PEG is a BNT162b2 and mRNA-1273 excipient. Owing to the similar chemical structures of PS80 and PEG, their cross-reactivity increasing the risk of vaccine-related allergies in patients who have previously experienced an allergy to either of

Table I. Previously reported cases of fixed drug eruption following COVID-19 vaccination

No.	Author	Sex/age	Vaccine	Dose	Time of onset	Affected region	Intradermal test	Patch test
1	Mintoff et al[2]	F/26	BNT162b2 BNT162b2	1st 2nd	15 d 14 d	Shoulder	Not performed	Not performed
2	Lellig et al[3]	F/54	BNT162b2 BNT162b2	1st 2nd	24 h 4 d	Wrist	Not performed	(+) on BNT162b2 and polyethylene glycol
3	Wantavorn-prasert et al[4]	M/74	AZD1222	1st	25 h	Trunk, both extremities	Not performed	Not performed
4	Salem et al[5]	F/41	AZD1222	1st	3 d	Shoulder	Not performed	Not performed
5	Kong et al[6]	M/66	mRNA-1273	2nd	24 h	Trunk, both legs	Not performed	Not performed
6	This case	M/50	AZD1222 AZD1222 mRNA-1273	1st 2nd 3rd	24 h 24 h 24 h	Nape, trunk, both extremities, penis	(+) on polysorbate 80 and polyethylene glycol	(+) on polysorbate 80 and polyethylene glycol

the materials is a concern.[7] Excipient-related type I hypersensitivity has been widely investigated in COVID-19 vaccines, and 1 study demonstrated uneventful AZD1222 vaccination in 8 patients with a PEG allergy.[7-9] However, little is known about vaccine excipient-related type IV hypersensitivity.

Type IV hypersensitivity is a major FDE pathophysiology in which medication antigens activate the resident epidermal memory of $CD8^+$ T cells and subsequently cause immunologic damage to keratinocytes and melanocytes.[10] Resident memory T cells have been implicated in recurrent FDE at the same site.[10] Because our case showed an identical reaction following the administration of AZD1222 and mRNA-1273, the common antigen between the 2 vaccines would be considered to trigger type Ⅳ hypersensitivity and subsequent FDE. Two components could be considered: SARS-CoV-2 virotopes and cross-reactivity of the excipients. Although 2 reports of FDE with AZD1222 have considered vaccine virotopes as a causative factor, IDT and a patch test were not performed in both the studies.[4,5] Furthermore, if SARS-CoV-2 virotopes were the FDE-causative antigens, FDE-like eruption would have also been reported in patients with COVID-19. Furthermore, considering the positive reaction in the patch test and IDT, the cross-reactivity of PS80 and PEG is more likely regarded as a recurrent FDE triggering factor following vaccination.

We report a case of recurrent FDE following vaccination with AZD1222 and mRNA-1273, suggesting the cross-reactivity of the excipients as a causative factor.

Conflicts of interest

None disclosed.

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