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Generalized Bullous Fixed Drug Eruption after ChAdOx1 nCoV-19 Vaccination

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Dear Editor,

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A 74-year-old Thai male presented with a rash appearing 25 hours after receiving the first dose of the adenoviral-vectored COVID-19 vaccine, ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca). These lesions abruptly appeared without any accompanying symptoms. The patient's medical history included end stage renal disease, atrial fibrillation, and ischemic stroke. The patient denied taking any new drugs, supplements or food that had not previously consumed prior to this cutaneous eruption.

Upon examination, multiple well-defined round to oval erythematous to violaceous plaques with central dusky appearance and bullous formation were found on the trunk and both extremities (Figure 1). There was no mucosal involvement. Punch biopsy was performed. Histopathology was consistent with bullous fixed drug eruption (Figure 2). Laboratory work up showed no definite internal organ involvement.

Given the clinical and histological features, a diagnosis of generalized bullous fixed drug eruption (GBFDE) was made. Fixed drug eruption (FDE) typically presents within one to two weeks after the initial exposure, and less than two days for the subsequent episodes. In contrast, GBFDE occurs with more sudden onset and typically within twenty-four hours.¹ Based on the temporal relationship, the ChAdOx1 nCoV-19 vaccine was considered as the eruption trigger. Naranjo adverse drug reaction probability scale was 5 (probable).

Patch testing on residual hyperpigmented area after FDE resolution was considered as a method to confirm the culprit drug. Unfortunately, testing could not be performed due to limited access to the vaccine and hospital areas during the COVID-19 pandemic. Alternatively, an interferon (IFN) gamma (γ) enzyme-linked immunospot (ELISpot) assay was undertaken. This technique assesses the amount of IFN- γ production from peripheral blood mononuclear of subjects upon stimulation with the suspected agents. In this case, polysorbate80 (concentration 1:2000 and 1:10000), the excipient of the vaccine, was tested and yielded negative results. Our patient also reported receiving an annual influenza vaccination which contains similar excipient (polysorbate) without any adverse reactions. This fact may support that his GBFDE is a result of a hypersensitivity reaction to the ChAdOx1 nCoV-19, not the excipient.

Several vaccines have been implicated to trigger FDE, including combined pentavalent DTaP-IPV-Hib vaccine, yellow fever, influenza, Human Papilloma Virus, recombinant adjuvanted Zoster vaccine, and COVID-19 vaccines.²⁻⁵ Although FDE is usually self-limited and has a

favorable prognosis, GBFDE is considered a severe cutaneous adverse reaction (SCAR) with a high mortality rate among the elderly.¹ Only seven cases of COVID-19 vaccination-associated SCAR have been documented despite their wide use (summarized in Table 1).

The current GBFDE treatment is cessation of the causative agents and supportive care.¹ The patient was treated with topical 0.25% desoximethasone cream. The lesions gradually resolved within two weeks leaving post-inflammatory hyperpigmentation.

To our knowledge, this is the first report of ChAdOx1 nCoV-induced GBFDE. Because of the potential recurrence of SCAR, the patient was advised to switch to a different COVID-19 vaccine platform.

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Figure legends

Figure 1 Physical examination showed multiple round- to oval-shaped erythematous to violaceous patches with central dusky appearance on trunk and extremities (a, b, d). large and well-demarcated central erosions were also noted on the axilla and trunk (c), right forearm (d), and right

leg (e). No mucosal lesions were observed and the lesions were found in more than two different sites of the body.

Figure 2 Punch biopsy was performed from the lesion on his back (a) Subepidermal separation with superficial and deep perivascular inflammatory cells infiltration (Haematoxylin–eosin stain, 50x). (b) Mixed inflammatory cells infiltrate, composing of lymphohistiocytes and numerous eosinophils. Melanophages were seen in the upper dermis. (Haematoxylin–eosin stain, 200x)

Table 1 Reported cases of severe cutaneous adverse reactions (SCARs) due to COVID-19 vaccine administration

Case	Sex	Age	Allergy	Vaccine platform	First/Second dose	Timing of onset	Lag period after vaccination	Clinical phenotype	Supporting investigations	Outcome	Second dose administration
1	M	74	Sulfa drugs, amoxicillin-clavulanic acid	viral vector vaccine (Janssen, Ad26.COV2.S)	First	3 days	10 days	AGEP	Blood test: leukocytosis with neutrophilia and eosinophilia, normal creatinine level and liver enzymes Histology: epidermal spongiosis with subcorneal neutrophilic pustules and dermal neutrophilic inflammation with eosinophils DIF: negative	Improved with oral prednisolone 20 mg/day and topical steroid	NA
2	F	43	NA	viral vector vaccine (Oxford-AstraZeneca, ChAdOx1)	First	3 days	NA	AGEP	Blood test: leukocytosis with eosinophilia Histology: Lichenoid interface dermatitis, intracorneal pustules, lymphocytic infiltrate with numerous eosinophils	Resolution with topical corticosteroid within 30 days	Change platform to mRNA vaccine (Pfizer/BioNTech, BNT162b2), no recurrence of reaction
3	F	32	No	viral vector vaccine (Oxford-AstraZeneca, ChAdOx1)	First	3 weeks	NA	AGEP	Blood test: leukocytosis with neutrophilia	Resolution with short course systemic corticosteroid within 2 weeks	Not mentioned
4	M	38	NA	mRNA vaccine	Second	5 days	NA	AGEP	Blood test: marked	Resolution with topical	NA

				(Pfizer/BioNTech, BNT162b2)					neutrophilia Histology: supportive of the diagnosis of AGEp	mometasone cream	
5	M	60	NA	viral vector vaccine (Oxford-AstraZeneca, ChAdOx1)	First	3 days	7 days	SJS	Histology: moderate intraepidermal infiltration of lymphocytes and neutrophils with moderate spongiosis, scattered degenerated apoptotic keratinocytes, patchy areas of basal cell degeneration and interface dermatitis, perivascular and periadnexal inflammatory cell infiltrate along with extravasation of erythrocytes in dermis	Complete resolution with oral cyclosporine 300 mg/day after 7 days	Change platform, no available data on outcome
6	F	Middle-aged	No	mRNA vaccine (Pfizer/BioNTech, BNT162b2)	Second	5 days	NA	SJS	NA	Treated with oral prednisolone 30 mg/day with unknown outcome	NA
7	F	49	NA	mRNA vaccine (Pfizer/BioNTech, BNT162b2)	First	7 days	NA	TEN	Histology: full-thickness epidermal necrosis along with dermal-epidermal separation and necrotic keratinocytes	Complete resolution with 2 doses of etanercept 50 mg/ml (on day1 and day 3) after 22 days	Not mentioned
8	M	66	No	mRNA vaccine (Moderna, mRNA-1273)	Second	24 hours	5 days	GBFDE	Blood test: anti-BP180 negative (8), anti-BP230	Improved with high-dose oral prednisone	NA

									negative (< 2) Histology: full-thickness epidermal necrosis and a very sparse lymphocytic inflammatory infiltrate		
9 (Our case)	M	74	Penicillin (swollen lips)	viral vector vaccine (Oxford-AstraZeneca, ChAdOx1)	First	25 hours	2 days	GBFDE	Histology: subepidermal separation with superficial and deep perivascular mixed inflammatory cells infiltration composing lymphohistiocytes and numerous eosinophils, melanophages were seen in the upper dermis IFN- γ ELISpot assay: negative for polysorbate 80	Resolution with residual hyperpigmentation with topical desoximetasone within 2 weeks	Change platform, no available data on outcome

AGEP: acute generalised exanthematous pustulosis

SJS: Steven-Johnson syndrome

TEN: Toxic epidermal necrolysis

GBFDE: generalized bullous fixed drug eruption

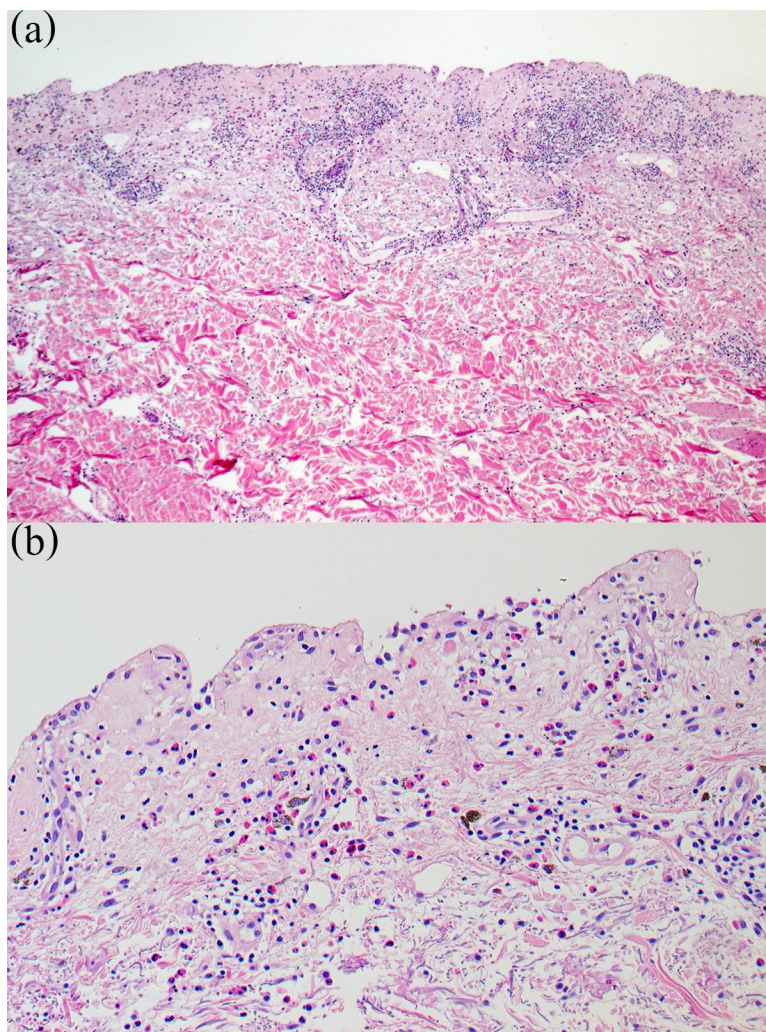
DIF: direct immunofluorescence study

IFN- γ ELISpot: interferon gamma enzyme-linked immunospot

NA: not applicable



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