Cutaneous lupus erythematosus flare with vitiligo-like depigmentation following the AstraZeneca COVID vaccine

Farrah Bakr, MBBS, MRCP,[a] James Denny, MBChB, MRCP,[a] Parastoo Babakinejad, MBBS, MRCP,[a] Andrew Giles, MBBS,[b] and Hélène du Peloux Menagé, MBBS, MRCP[a]

Key words: cutaneous lupus; COVID-19; vaccine.

INTRODUCTION

The recent COVID-19 pandemic has had a profound impact on global health. The importance of clinician awareness of the dermatological manifestations of the disease is paramount.[1] In addition, the onset of vaccination programs to combat the disease is uncovering further cutaneous eruptions and systemic reaction patterns.[2] We present a case of cutaneous lupus in a patient with underlying secondary Sjögren's syndrome following the Oxford–AstraZeneca COVID-19 vaccine (AZD1222), review the literature and highlight the potential for systemic lupus erythematosus or cutaneous lupus erythematosus (CLE) flare following COVID vaccination.

Abbreviations used:

ANA:	antinuclear antibody
Anti-dsDNA:	anti-double stranded DNA
Anti-Sm:	anti Smith
CLE:	cutaneous lupus erythematosus
IFN:	interferon
MCTD:	mixed connective tissue disease
RS:	Rowell's syndrome
SCLE:	subacute cutaneous lupus erythematosus
SLE:	systemic lupus erythematosus
TLR:	toll-like receptors

CASE REPORT

A 51-year-old gentleman with a diagnosis of systemic lupus erythematosus (positive dsDNA [anti double stranded DNA] and ANA titers) with overlapping features of Sjögren's disease (parotid swelling, Ro and La antibody positivity, recurrent pleuropericardial effusions, and bronchiectasis) managed with hydroxychloroquine and azathioprine presented to dermatology in April 2021 with a widespread pruritic eruption. Onset was 1 week after receiving the Oxford–AstraZeneca COVID-19 vaccine (AZD1222) (January 2021), with subsequent exacerbation 4 days after the second dose, 2 months later; managed by his family physician with prednisolone 30 mg for 5 days. The patient was not started on any new medications prior to the onset of the eruption and had not displayed cutaneous lupus features in the past.

On presentation, he exhibited indurated, flat-topped papular lesions on the scalp, dorsal hands, ears and erythematous, polycyclic, annular lesions on the arms, back, scalp and trunk suspicious for discoid, and subacute CLE, respectively (Fig 1, *A-D*). Palmar perniosis was noted.

Punch biopsies from the back and dorsa of the hand demonstrated features consistent with CLE including vacuolar interface dermatitis with pigmentary incontinence, apoptotic keratinocytes, and an inflammatory lymphocytic infiltrate in the superficial dermis (Fig 2, *A* and *B*). Direct immunofluorescence from a non–sun-exposed site on the back revealed immunoglobulin G anti-nuclear antibodies throughout the epidermis (red) with C3 deposition (green) in the basement membrane (Fig 3, *A*). An

From the Department of Dermatology, University Hospital Lewisham, London, United Kingdom[a]; and Department of Histopathology, University Hospital Lewisham, London, United Kingdom.[b]

Funding sources: None.

IRB approval status: Not applicable.

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

Correspondence to: Farrah Bakr, MBBS, MRCP, Department of Dermatology, University Hospital Lewisham, Lewisham High St, London SE13 6LH, United Kingdom. E-mail: farrahbakr@doctors.org.uk.

JAAD Case Reports 2022;30:51-5.

2352-5126

https://doi.org/10.1016/j.jdcr.2022.10.003

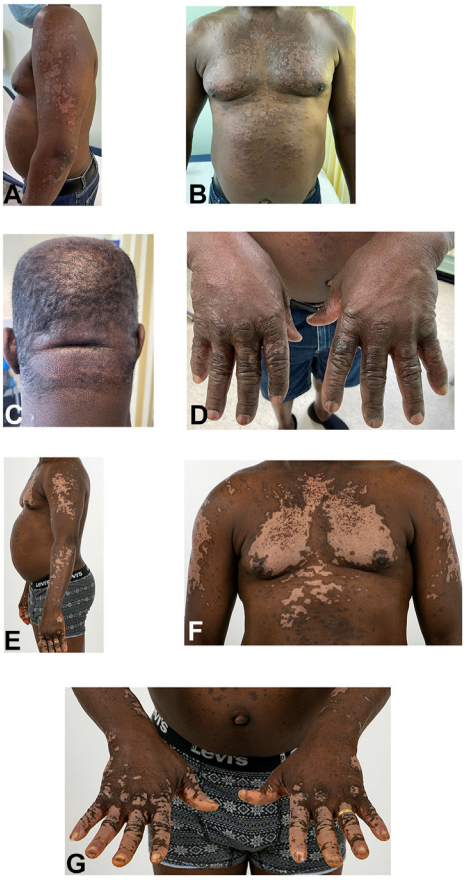

Fig 1. Widespread polycyclic annular lesions on the arms, trunk scalp, and hands in a patient 4 days after receiving the second dose of the Oxford–AstraZeneca COVID-19 vaccine (AZD1222) (**A-D**). Resolution of the acute eruption resulted in extensive vitiligo-like post inflammatory depigmentation (**E-G**).

autoimmune screen revealed positive ANA titers, as previously. Anti-Ro/SSA and anti-Sm antibodies (anti Smith antibody) were positive, in keeping with the patient's history of Sjögren's-like features, as well as a chronically raised erythrocyte sedimentation rate and neutropenia. His renal function was unremarkable. He reported no systemic symptoms.

A diagnosis of Oxford-AstraZeneca COVID-19 vaccine (AZD1222) induced CLE was made in view of the clinical features, histology, direct immunofluorescence, and antibody profile. Hydroxychloroquine dosage was increased from 200 mg to 400 mg and azathioprine from 100 mg to 150 mg daily. At 6 months, the acute eruption had resolved leaving widespread post-inflammatory hypopigmentation with areas of vitiligo-like post inflammatory depigmentation (Fig 1, *E-G*). At further follow-up there is evidence for repigmentation within some of the lesions.

DISCUSSION

Cutaneous eruptions following COVID-19 infection are not uncommon. Although the exact incidence is yet to be ascertained, cutaneous manifestations have been reported in up to 20% of cases[3] and can encompass a wide range of morphologies including urticarial, morbilliform, papulovesicular, chilblain-like, livedoid, and vasculitic.[1] Far less commonly (<0.5% of cases), a wide range of cutaneous eruptions have also been reported post-COVID-19 vaccination but these are more often associated with the mRNA vaccines (BNT162b2 Pfizer-BioNTech and mRNA-1273 Moderna). Pityriasis rosea, urticaria, and chilblain-like lesions are the most frequently observed morphologies (0.1% to 0.4% of cases); whereas, morbilliform and petechial eruptions (<0.1% of cases) have been associated with adenoviral vector vaccines.[2]

CLE following COVID-19 vaccination is uncommon. Our case is only the second reported after exposure to the Oxford–AstraZeneca adenoviral vaccine (AZD1222),[4] with the majority of remaining cases reported after exposure to the Pfizer mRNA vaccine (BNT162b2).[4-12] The summary of CLE eruptions occurring post-COVID vaccination is summarized in Table I. The postulated mechanism behind CLE eruption following COVID-19 vaccination involves increased Type 1 interferon (IFN) secretion. In the pathogenesis of cutaneous lupus this is triggered by the binding of immune complexes to toll-like receptors on dendritic cells. Both mRNA and adenoviral COVID-19 vaccines trigger innate sensors leading to Type 1 IFN secretion,[13] resulting in cytokine and chemokine cascades, T-cell activation, and a lichenoid tissue reaction (Fig 3, *B*). Interestingly, the majority of cases are associated with anti-Ro and anti-La antibodies, which are often newly positive.[4,7,8,10,11] Anti-Ro antibodies are encountered in up to 70% of non-vaccine associated subacute CLE cases. Furthermore, anti-Ro and/or anti-La positivity is also associated with an increased IFN signature.[14]

The vitiligo-like depigmentation is an unusual and interesting feature with some evidence of repigmentation at follow-up. Cases of vitiligo post-COVID vaccination have been reported in the literature[16] and may again be related to type 1 IFN production which is also an early phase in vitiligo pathogenesis.[17]

In summary, we present a case of CLE following the Oxford–AstraZeneca COVID-19 vaccine

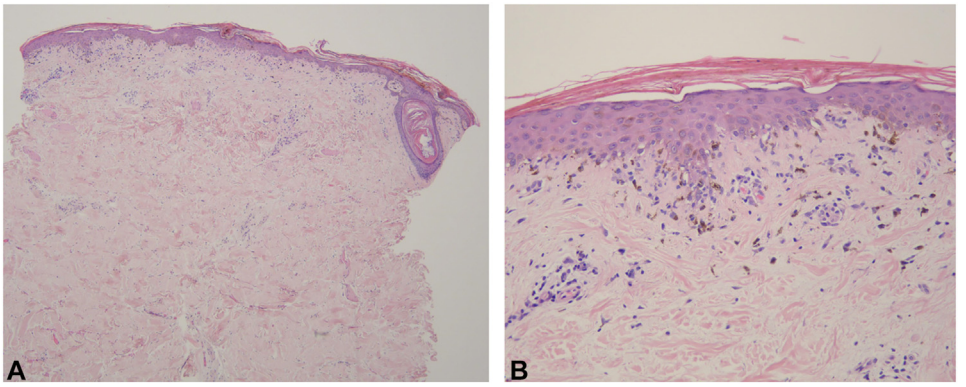

Fig 2. Histological features consistent with cutaneous lupus. **A,** low power magnification reveals mild inflammatory predominantly lymphocytic infiltrate in the superficial dermis with pigmentary incontinence. There is mild irregular acanthosis of the epidermis with a plugged follicle on the right. (hematoxylin and eosin, ×40). **B,** at higher magnification there is further evidence of an interface dermatitis with prominent vacuolar degeneration of the basal epidermis with several apoptotic keratinocytes. There is marked pigmentary incontinence in the superficial dermis with a mild, mainly lymphocytic inflammatory infiltrate. (hematoxylin and eosin, ×200).

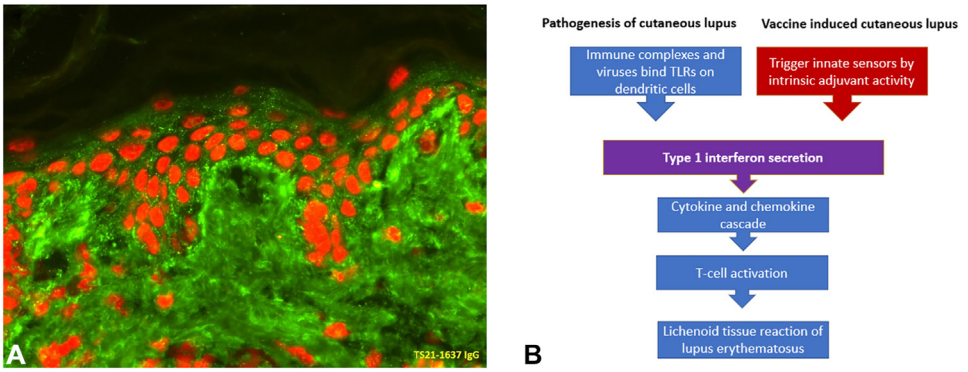

Fig 3. A, direct immunofluorescence reveals immunoglobulin G antibodies throughout the epidermis (*red*) with C3 deposition (*green*) in the basement membrane consistent with connective tissue disease. **B,** postulated mechanism of vaccine-induced cutaneous lupus. COVID-19 vaccines trigger innate sensors which lead to type 1 interferon secretion, resulting in the activation of cytokine and chemokine cascades. T-cell activation ensues followed by a lichenoid tissue reaction. *TLRs*, Toll-like receptors

Table I. Summary of reported cutaneous lupus reactions occurring post-COVID vaccination

Patient	Age (years)	Sex	Autoimmune disease history	COVID vaccine type	CLE subtype	Induction or exacerbation of CLE	Onset of skin lesions post-vaccine (days)	Antibody profile	Reference
1	74	F	Nil	mRNA (BNT162b2)	SCLE	Induction	1	ANA (1:640) Anti-Ro, anti-La	Gambichler et al[5]
2	73	F	SCLE	mRNA (BNT162b2)	SCLE	Exacerbation	10	Anti-Ro	Niebel et al[6]
3	62	F	SCLE	Adenoviral (AZD1222)	SCLE	Exacerbation and systemic transformation	10	ANA (1:640) anti-Ro, anti-La	Kreuter et al[4]
4	54	F	SCLE	mRNA-1273 (Moderna)	SCLE	Exacerbation	4	ANA (1:1280) anti-dsDNA, anti-Sm	Joseph et al[15]
5	70	M	Nil	mRNA (BNT162b2)	SCLE	Induction	10 wk	ANA (1:540) anti-Ro	Liu et al[10]
6	79	M	Nil	mRNA (BNT162b2)	SCLE	Induction	10	ANA (1:320) anti-Ro, anti-La	Kreuter et al[7]
7	30	F	Primary biliary cholangitis	mRNA (BNT162b2)	SCLE	Induction	10	Anti-dsDNA, anti-Sm, anti-nRNP anti-Ro, anti-La	Zengarini et al[11]
8	41	M	MCTD	mRNA (BNT162b2)	RS	Induction	4	Speckled ANA	Niebel et al[12]
9	22	F	Hypothyroidism	mRNA-1273 (Moderna)	Drug-induced SCLE mimicking RS	Induction	10	ANA (1:80)	Niebel et al[12]
10	24	F	SLE	mRNA (BNT162b2)	SCLE	Induction	14	Anti-dsDNA, anti-Sm, anti-histone La	Rechtien et al[8]
11	33	F	Nil	mRNA (BNT162b2)	SCLE	Induction	1	Nil	Rose et al[9]
12	51	M	SLE and Sjogren's overlap	Adenoviral (AZD1222)	DLE and SCLE	Induction	7	ANA (1:1280) Anti-dsDNA, anti-Sm anti-Ro, anti-La	Present case

ANA, Antinuclear antibody; *Anti-dsDNA*, anti-double stranded DNA; *anti-Sm*, anti-Smith antibody; *F*, Female; *M*, Male; *MCTD*, mixed connective tissue disease; *SCLE*, subacute cutaneous lupus erythematosus; *SLE*, systemic lupus erythematosus; *RS*, Rowell's syndrome.

(AZD1222) with subsequent vitiligo-like depigmentation. Decisions as to further vaccination were made on a personalized risk benefit analysis and a subsequent dose of Pfizer mRNA vaccine (BNT162b2) was well tolerated.

Conflicts of interest

None disclosed.

REFERENCES

1. Genovese G, Moltrasio C, Berti E, Marzano AV. Skin manifestations associated with COVID-19: current knowledge and future perspectives. *Dermatology*. 2021;237(1):1-12. https://doi.org/10.1159/000512932
2. Temiz SA, Abdelmaksoud A, Wollina U, et al. Cutaneous and Allergic reactions due to COVID-19 vaccinations: a review. *J Cosmet Dermatol*. 2022;21:4-12. https://doi.org/10.1111/jocd.14613
3. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. *J Eur Acad Dermatol Venereol*. 2020;34(5):e212-e213. https://doi.org/10.1111/jdv.16387
4. Kreuter A, Burmann SN, Burkert B, Oellig F, Michalowitz AL. Transition of cutaneous into systemic lupus erythematosus following adenoviral vector-based SARS-CoV-2 vaccination. *J Eur Acad Dermatol Venereol*. 2021;35(11):e733-e735. https://doi.org/10.1111/jdv.17514
5. Gambichler T, Scholl L, Dickel H, Ocker L, Stranzenbach R. Prompt onset of Rowell's syndrome following the first BNT162b2 SARS-CoV-2 vaccination. *J Eur Acad Dermatol Venereol*. 2021;35(7):e415-e416. https://doi.org/10.1111/jdv.17225
6. Niebel D, Ralser-Isselstein V, Jaschke K, Braegelmann C, Bieber T, Wenzel J. Exacerbation of subacute cutaneous lupus erythematosus following vaccination with BNT162b2 mRNA vaccine. *Dermatol Ther*. 2021;34(4):e15017. https://doi.org/10.1111/dth.15017
7. Kreuter A, Licciardi-Fernandez MJ, Burmann SN, Burkert B, Oellig F, Michalowitz AL. Induction and exacerbation of subacute cutaneous lupus erythematosus following mRNA-based or adenoviral vector-based SARS-CoV-2 vaccination. *Clin Exp Dermatol*. 2022;47(1):161-163. https://doi.org/10.1111/ced.14858
8. Rechtien L, Erfurt-Berge C, Sticherling M. SCLE manifestation after mRNA COVID-19 vaccination. *J Eur Acad Dermatol Venereol*. 2022;36(4):e261-e263. https://doi.org/10.1111/jdv.17895
9. Rose C, Apgar R, Green M. Cutaneous lupus-erythematosus-like reaction arising after COVID-19 vaccination. *J Cutan Pathol*. 2022;49(11):943-946. https://doi.org/10.1111/cup.14281
10. Liu V, Messenger NB. New-onset cutaneous lupus erythematosus after the COVID-19 vaccine. *Dermatol Online J*. 2021;27(11). https://doi.org/10.5070/D3271156093
11. Zengarini C, Pileri A, Salamone FP, Piraccini BM, Vitale G, La Placa M. Subacute cutaneous lupus erythematosus induction after SARS-CoV-2 vaccine in a patient with primary biliary cholangitis. *J Eur Acad Dermatol Venereol*. 2022;36(3):e179-e180. https://doi.org/10.1111/jdv.17827
12. Niebel D, Wilhelmi J, De Vos L, et al. Annular plaques mimicking Rowell's syndrome in the course of coronavirus disease 2019 mRNA vaccines: an overlooked phenomenon? *J Dermatol*. 2022;49(1):151-156. https://doi.org/10.1111/1346-8138.16210
13. Teijaro JR, Farber DL. COVID-19 vaccines: modes of immune activation and future challenges. *Nat Rev Immunol*. 2021;21(4):195-197. https://doi.org/10.1038/s41577-021-00526-x
14. Wither J, Johnson SR, Liu T, et al. Presence of an interferon signature in individuals who are anti-nuclear antibody positive lacking a systemic autoimmune rheumatic disease diagnosis. *Arthritis Res Ther*. 2017;19(1):41. https://doi.org/10.1186/s13075-017-1243-y
15. Joseph AK, Chong BF. Subacute cutaneous lupus erythematosus flare triggered by COVID-19 vaccine. *Dermatologic Therapy*. 2021;34(6):e15114. https://doi.org/10.1111/dth.15114
16. Herzum A, Micalizzi C, Molle MF, Parodi A. New-onset vitiligo following COVID-19 disease. *Ski Heal Dis*. 2022;2(1):e86. https://doi.org/10.1002/ski2.86
17. Bertolotti A, Boniface K, Vergier B, et al. Type I interferon signature in the initiation of the immune response in vitiligo. *Pigment Cell Melanoma Res*. 2014;27(3):398-407. https://doi.org/10.1111/pcmr.12219