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Diffuse cutaneous systemic sclerosis following SARS-Co V-2 vaccination

Alice Cole [a], Rhys Thomas [b], Nina Goldman [a], Kevin Howell [b], Kuntal Chakravarty [b], Christopher P. Denton [a], Voon H. Ong [a,*]

[a] UCL Centre for Rheumatology and Connective Tissue Diseases, London, UK
[b] Royal Free London NHS Foundation Trust, London, UK

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ABSTRACT

The largest world-wide vaccination rollout ever is currently underway to tackle the covid-19 pandemic. We report a case of diffuse cutaneous systemic sclerosis (SSc) in a 70-year-old male with rapidly progressive skin thickening which developed two weeks after receiving the first dose of the ChAdOx1 nCOV-19 vaccine. As the onset of SSc skin was in close temporal proximity to the administration of the first dose vaccine with no other triggers, we suspected a possible adverse reaction to the ChAdOx1 nCOV-19 vaccine. We hypothesise that the recombinant adenoviral vector encoding the spike protein antigen of SARS-CoV-2 triggered an unexpected immune activation resulting in an atypical presentation of late-onset SSc, within the well-recognised ANA positive, ENA negative subgroup of patients.We review the possible mechanisms underlying autoimmunity when provoked by vaccination and other published rheumatological phenomenon occurring shortly after COVID vaccination.

The largest world-wide vaccination rollout ever is currently underway to tackle the covid-19 pandemic. A number of immunological sequalae of the SARS-Co V-2 vaccination have been observed [1].

We report a case of diffuse cutaneous systemic sclerosis (SSc) in a 70-year-old male with rapidly progressive skin thickening developed two weeks after receiving the first dose of the ChAdOx1 nCOV-19 vaccine. There were no features of SSc prior to vaccination. The patient was a current smoker with evidence of emphysema on cross sectional imaging and did not have any known exposure to toxic compounds. The assessment values highlighted below were performed six months after initial symptom onset.

His disease was active with high skin score as assessed by modified Rodnan Skin Score (mRSS) 47/51 with multiple inflammatory ulcers over his proximal limbs (Fig. 1). Interestingly, the patient did not describe Raynaud's phenomenon of the digits, nor did the ulcers affect his digits, however nailfold capillaroscopy demonstrated tortuous capillaries, mild dilatation and dropout (Fig. 1). Electromyography revealed an active myositis. High resolution computed tomography did not demonstrate any interstitial lung disease. CT abdomen and pelvis showed no malignancy and therefore, no endoscopic evaluation was considered. Cardiac magnetic resonance imaging showed normal T2 signals and preserved ventricular function. The results are not specific for primary SSc heart involvement however, in combination with a raised troponin T (82 ng/L) and brain natriuretic peptide (744 ng/L) are consistent with a degree of myocarditis contributing towards the clinical picture.

Immunological testing demonstrated anti-nuclear antibody (HEp-2 ANA) 1:5120 homogenous staining. There was no SSc-specific reactivity. Other autoantibodies including double stranded DNA, anti-neutrophil cytoplasmic antibody (ANCA) and anti-phospholipid antibody screen were negative. Eosinophils were raised at 1.29 x10^9/litre on admission. SARS-Co V-2 Total antibody 'Spike S' was detected at low level, 3.5 U/ml and nucleocapsid N-protein was negative. After discussion at the hospital Vaccine Safety Committee, the decision was made that the potential benefits of a second dose of vaccine would be outweighed by the potentially devastating effects of a further severe idiosyncratic vaccination reaction.

As the onset of SSc skin was in close temporal proximity to the administration of the first dose vaccine with no other triggers, we suspected a possible adverse reaction to the ChAdOx1 nCOV-19 vaccine. We hypothesise that the recombinant adenoviral vector encoding the spike protein antigen of SARS-CoV-2 triggered an unexpected immune activation resulting in an atypical presentation of late-onset SSc, within the well-recognised ANA positive, extractable nuclear antibody (ENA)

* Corresponding author. Clinical Lecturer in Rheumatology, UCL Centre for Rheumatology and Connective Tissue Diseases, Royal Free Campus, Rowland Hill Street, London, NW3 2PF, UK.
E-mail address: v.ong@ucl.ac.uk (V.H. Ong).

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negative subgroup of patients.

There are numerous reports of inflammatory adverse events (AE) following SARS-Co V-2 vaccination which range from short-lived or localised inflammatory events to development of more sustained autoimmune disease [2]. It has been proposed that the mechanisms by which autoimmunity occurs in this setting could include molecular mimicry and 'the bystander effect'. Molecular mimicry can occur if the shared peptide sequences of the vaccine nucleoprotein/spike protein and self-antigens leads to autoantibody formation. An accompanying theory is that the virus spike protein or the intrinsic adjuvant activity of the vaccine may deliver an antigenic signal with aberrant activation of antigen presenting cells with production of pro-inflammatory mediators [3]. TLR-9 is the major double-stranded DNA sensor for the adenoviral vaccine and endosomal TLR9-driven B cell receptor-activated B cells, when unconstrained is implicated in class-switched autoantibody production and an inflammatory amplification loop [4,5]. This aligns with local elevation of TLR-9 signature in lesional SSc skin that associates with profibrotic phenotype via autocrine TGFβ induction [6].

In cases developing a defined disease such as SSc, it is likely that a permissive genetic background susceptibility is relevant and may for example reflect one or more, as yet undefined, rare genetic variants [7].

Recently, IgG autoantibodies targeting autoantigens associated with SSc were identified in covid-19 infection. Notably these autoantibodies were temporally associated with anti-SARS-CoV-2 IgG responses suggesting the potential broad B cell responses are shared in pathogenesis of both covid-19 infection and vaccine responses [3].

To assess the risk of autoimmunity following vaccine or infection, data on autoimmune aetiologies are collected via the national authorities. The US Vaccine Adverse Event Reporting System data attests to the safety of the covid-19 vaccine and autoimmune conditions with the exception of immune thrombocytopaenia [8].

The World Health Organization (WHO) reported that 8,200,642,671 doses of vaccines against SARS-CoV-2 have been administered worldwide [9]. Pharmacovigilance databases [10,11] are established to identify safety concerns. These are large-scale case series, which enable post marketing surveillance, and are especially useful for rare events. Individual case reports as shown in Table 1 further demonstrate the link between rheumatological disease and vaccination but large-scale prospective surveillance registers can provide key data in comparative estimations of risk.

To our knowledge this is the first described case of SSc precipitated by SARS-Co V-2 vaccination. This should not detract from the importance of the vaccination rollout given the low incidence of post-vaccination autoimmunity however, exploring the shared mechanisms for autoimmunity between Sars-Co V-2 vaccine and infection may offer further insight into the aetiopathogenesis of SSc [12].

Author statement

Alice Cole: Conceptualization, Writing – original draft, Writing – review & editing, Supervision, **Rhys Thomas**: Conceptualization, Writing – original draft, Writing – review & editing, Supervision, **Christopher Denton**: Conceptualization, Writing – original draft, Writing – review & editing, Supervision, **Voon Ong**: Conceptualization, Writing – original draft, Writing – review & editing, Supervision, **Kuntal Chakravarty**,: Writing – review & editing, **Nina Goldman**: Writing – review & editing, **Kevin Howell**: Investigation.

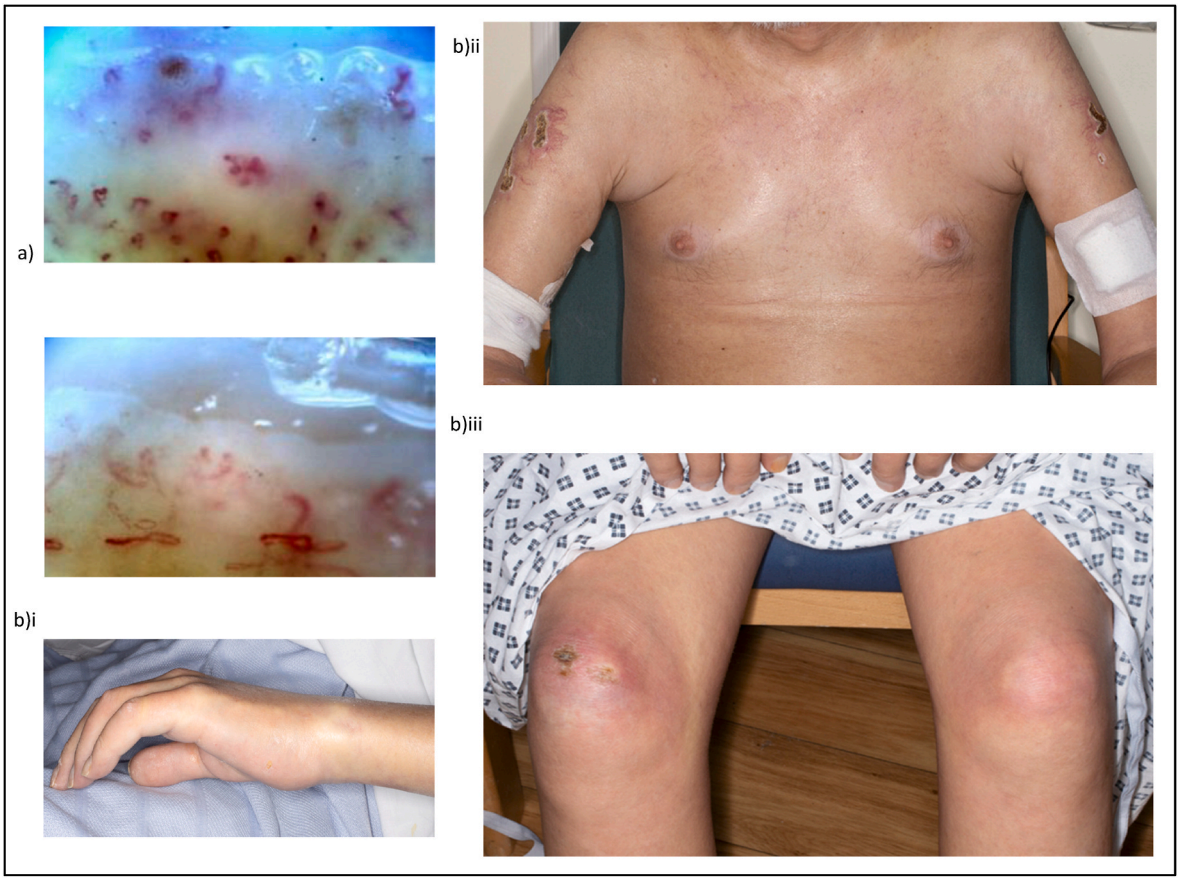

Fig. 1. a) Capillaroscopy demonstrating abnormal capillaries. b) i. Left hand contracture with restricted wrist mobility; ii. Inflammatory ulcers over upper limbs and diffuse skin involvement of anterior chest wall and abdomen; iii. Ulcer over right knee with skin thickening over both legs.

Table 1
Immune-mediated rheumatological phenomena observed following SARS-Co V-2 vaccination.

Condition	N =	Age	Sex F:M	New/ Flare	Median period of latency	mRNA/ Pfizer/ Moderna	Vector (n) Astrazeneca/ Covishield	Underlying autoimmune disease	Autoantibodies	Treatments	Outcome	Reference
Rheumatological												
Reactive arthritis (ReA)	1	23	1:0	N	3 days (1st dose)		1	Previous ReA	Negative	Intraarticular (IA) steroid injection	Mild disease, resolved	[13]
Transient synovitis	1	42	1:0	N	4 days (1st)	1		Previous episodes of synovitis	Negative (ANA, dsDNA)	Prednisolone 10 mg/ day	Moderate, fast response	[1]
Polymyalgia Rheumatica	1	70	0:1	N	3 days (1st)	1		nil	Negative	Prednisolone 40 mg/ day	Severe, rapid response	[1]
Remitting seronegative symmetrical synovitis with pitting oedema	1	83	1:0	N	7 days (1st)	1		Polymyalgia rheumatica, hypothyroid	Negative	Prednisolone 15 mg/ day	Severe, rapid response	[1]
Psoriatic Arthritis	1	36	1:0	N	10 days (1st)	1		Psoriasis only	No data	Ibuprofen 800 mg	Mid, rapid response	[1]
Systemic Lupus Erythematosus (SLE)	4	53	4:0	2 N 2F	10.5 days	1	3	Family history of autoimmune disease or history of SLE in flare patients	(ANA 1:320 dsDNA AMA m2 IgE 119 IU/ml)all new findings in one case	Prednisolone 50 mg, HCQ 400 mg, MMF 2g	1 severe case involving haemolysis [1] requiring rituximab with slow response. Others responded rapidly to treatment	[1,14]
Bechet's disease	4	33	0:4	4 F	7 days (1st) n = 3 2 days (2nd) n = 1	4		All had history of Bechets	No data	NSAIDS, colchicine and one case prednisolone	Moderate but rapid response	[1]
Rheumatoid arthritis (RA)	4	63	4:0	4 F	1.5 days (1st) 2.6 days (2nd)	4		Existing RA	ANA negative No change in seropositivity	Prednisolone or IA injection	Moderate with rapid response	[1]
Henoch Schonlein purpura	1	53	M	N	3 days (1st)	1		No relevant	Local IgA and C3 deposits on skin biopsy	Dexamethasone and prednisolone	Mild symptoms with rapid response	[1]
Neurosarcoid	1	43	M	F	3 days (1st)	1		History of neurosarcoid	No immunology	nil	Spontaneous resolution	[1]
Gout	1	70	M	F	1 day (1st) followed by another flare 1 day (2nd)	1		Gout, well controlled for 2 years prior	No immunology	Prednisolone 40 mg	Moderate with rapid response	[1]
Inflammatory Syndromes												
Capillary leak syndrome (CLS)	3	50	2:1	F	1.5 days (1st) 2 days (2nd)	2	1	History of systemic CLS	No immunology	IVIg and supportive management	Severe with one death	[15]
Multisystem inflammatory syndrome	8	36	3F:5 M	N	14 days (not specified)	3	2	Nil	ANA 1:40 (n = 1)	IVMP, 3 cases used IVIg	Severe with one death	[16–18]

Contributorship

A.C., R.T., N.G., K.C., C.D., V.O. contributed to the clinical care and investigations for the patient in this case. K.H. performed diagnostic capillaroscopy. A.C, R.T and V.O. took the lead in writing the manuscript. All authors provided critical feedback and helped shape the manuscript.

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Ethical approval information

The following report was written in accordance with local ethical guidelines and full informed consent was obtained from the patient, in line with submitting guidelines.

Data sharing statement

Not applicable.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Declaration of competing interest

None.

Data availability

No data was used for the research described in the article.

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