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Cutaneous symptoms of connective tissue diseases after COVID-19 vaccination: a systematic review

Dear Editor,

SARS-CoV-2 vaccination has been shown to substantially decrease COVID-19 morbidity and mortality.[1] However, reports have described the onset of autoimmune cutaneous symptoms after COVID-19 vaccination, usually in patients with pre-existing autoimmune diseases. No studies to date have analyzed the aggregate data. In this study, we systematically review cutaneous symptoms of connective tissue diseases after COVID-19 vaccination.

We searched PubMed/MEDLINE for articles in English published from December 11, 2020, to March 30, 2022, using key words "COVID-19 vaccin*" or "SARS-COV-2 vaccin*" and connective tissue disease-related search terms (e.g., "lupus," "systemic sclerosis," "scleroderma," "sclerotic skin," "dermatomyositis," "morphea"), yielding 126 articles (Figure 1). Screening and review of articles were completed according to Preferred Reporting Items for Systematic and Meta-Analysis (PRISMA) guidelines. Two independent reviewers (B.N. and M.J.L.) screened articles based on titles and abstracts to exclude duplicate, non-English, and review articles, yielding 116 reports. Of these, 30 articles (22 case reports, 3 case series, 2 cohort studies, 2 cross-sectional studies, and 1 clinical trial) encompassing 2020 patients (mean age 53.4 ± 19.9, 91.3% females) described 93 patients who developed post-vaccine cutaneous symptoms of connective tissue diseases.

The majority of affected patients had pre-existing autoimmune disease (77.4%, 72/93); new diagnosis of connective tissue disease after COVID-19 vaccination was uncommon (22.6%, 21/93). Females seemed to be affected more often (65.6%, 21/32), although the gender of most affected patients was not reported in larger studies.

The most common vaccines administered were Pfizer (60.5%, 1201/1984), Sinovac (19.6%, 388/1984), Moderna (10.8%, 215/1984), and AstraZeneca (9.1%, 180/1984). In non-case report and non-case series studies that described patients with and without cutaneous symptoms, the overall prevalence of cutaneous symptoms after vaccination ranged from 0.4% (1/265) to 4.4% (4/90), with a mean of 3.3% (65/1992) (Table 1).

The most common connective tissue diseases and cutaneous symptoms implicated after COVID-19 vaccination, when specified, were autoimmune sclerosing diseases (51.6%, 48/93), lupus (41.9%, 39/93), and dermatomyositis (6.5%, 6/93) (Table 2). When specified, 55.6% (45/81) of skin symptoms occurred after the 1st vaccine and 44.4% (36/81) after the 2nd

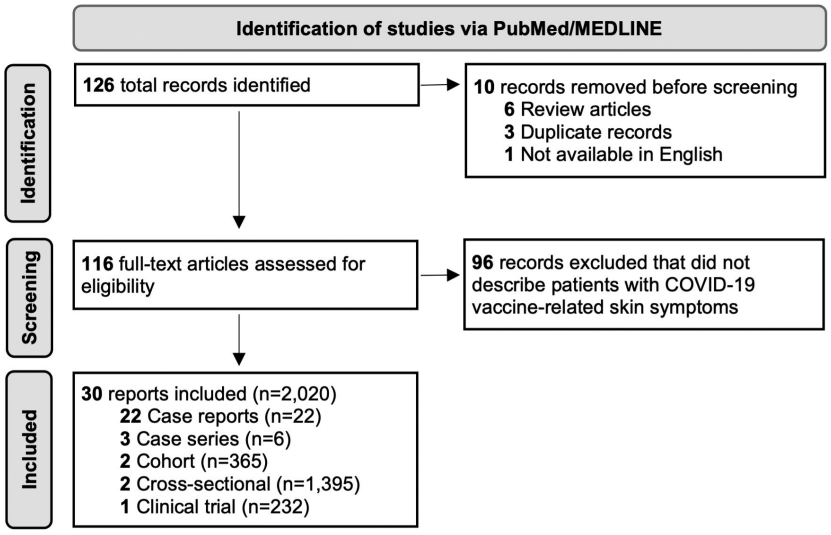

Figure 1 Flowchart of study identification via PubMed/MEDLINE according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

Table 1 Characteristics of non-case report and non-case series studies describing skin symptoms of connective tissue diseases after COVID-19 vaccination

Author, year, country	Study Design	Gender	Age[a](years)	Manufacturer of COVID-19 vaccine	History of autoimmune disease	Symptoms	Prevalence of skin symptoms	Exacerbation or new skin symptoms?
Cole et al. 2022; UK	Case report	1 M	70	1 AstraZeneca	Emphysema	*After 1st dose*: Skin thickening (1), skin ulceration (1)	100% (1/1)	100% (1/1) new onset SSc
Felten et al. 2021; France	Cross-sectional	669 F27 M	Median: 42 (34–51)	399 Pfizer 156 Sinovac 73 AstraZeneca 57 Moderna	SLE	Unspecified rash (12)	1.72% (12/696)	100% (12/12) exacerbations of SLE
Ferri et al. 2021; Italy	Cohort	236 F29 M	Mean: 57 ± 15	253 Pfizer 12 Moderna	SSc	Skin ulceration (1)	0.37% (1/265)	100% (1/1) exacerbation of SSc
Gambichler et al.	Case report	1 F	74	1 Pfizer	None	*After 1st dose*: Erythematous macules (1) and papules (1)	100% (1/1)	100% (1/1) new onset CLE
Gordon et al. 2022; US, France, Canada, UK, Australia, Mexico	Cross-sectional	616 F83 M	Mean: 62 ± 11	429 Pfizer 141 Moderna 104 AstraZeneca	SSc	*After 1st dose*: Unspecified rash (13), Raynaud's phenomenon (11) *After 2nd dose*: Unspecified rash (10), Raynaud's phenomenon (8)	*After 1st dose*: 3.43% (24/699) *After 2nd dose*: 2.58% (18/699)	100% (42/42) exacerbations of SSc
Gouda et al. 2022; Egypt	Case report	1 F	43	1 Pfizer	None	*After 2nd dose*: Pink-violaceous erythema (1), heliotrope rash (1)	100% (1/1)	100% (1/1) new onset DM
Hidaka et al. 2021; Japan	Case report	1 F	53	1 Pfizer	Vogt–Koyanagi–Harada disease, Hashimoto disease	*After 1st dose*: Purpura (1)	100% (1/1)	100% (1/1) new onset Evans syndrome associated with SLE
Jin et al. 2021; China	Case report	1 F	28	Not reported	SLE	*After 1st dose*: Eyelid edema (1)	100% (1/1)	100% (1/1) exacerbation of SLE
Joseph and Chong 2021; US	Case report	1 F	54	1 Moderna	SCLE	*After 1st dose*: Erythematous plaques (1) *After 2nd dose*: Malar rash (1)	100% (1/1)	100% (1/1) exacerbation of CLE
Kaur et al. 2022; US	Case report	1 M	54	1 Pfizer	Sjogren's syndrome	*After 2nd dose*: Purpura (1)	100% (1/1)	100% (1/1) new onset SLE
Kreuter et al. 2021; Germany	Case report	1 F	62	1 Oxford-AstraZeneca	SCLE	*After 1st dose*: Erythematous macules and patches (1)	100% (1/1)	100% (1/1) new onset SLE
Kreuter et al. 2021; Germany	Case report	1 M	79	1 Pfizer	Not reported	*After 1st dose*: Annular plaques (1)	100% (1/1)	100% (1/1) new onset CLE
Lee et al. 2022; Australia	Case report	1 M	53	1 Pfizer	None	*After 2nd dose*: Pink-violaceous erythema (1), crusted lesions (1)	100% (1/1)	100% (1/1) new onset DM
Lemoine et al. 2022; US	Case report	1 F	68	1 Pfizer	None	*After 1st dose*: Unspecified rash (1)	100% (1/1)	100% (1/1) new onset SLE
Liu et al. 2021; US	Case report	1 M	70	1 Pfizer	None	*After 2nd dose*: Erythematous plaques (1)	100% (1/1)	100% (1/1) new onset CLE

Table 1 Continued

Author, year, country	Study Design	Gender	Age[a](years)	Manufacturer of COVID-19 vaccine	History of autoimmune disease	Symptoms	Prevalence of skin symptoms	Exacerbation or new skin symptoms?
Metin and Cepeli 2022; Thailand and India	Case report	1 F	55	1 Pfizer	None	*After 2nd dose*: Erythematous, violaceous plaque (1)	100% (1/1)	100% (1/1) new onset morphea
Mousa N et al. 2022; Saudi Arabia	Case report	1 F	22	1 Pfizer	None	*After 1st dose*: Erythematous papules (1), hyperpigmentation (1)	100% (1/1)	100% (1/1) new onset SLE
Niebel et al. 2021; Germany	Case report	1 F	73	1 Pfizer	SCLE	*After 1st dose*: Erythematous patches (1)	100% (1/1)	100% (1/1) exacerbation of SCLE
Niebel et al. 2022; Germany	Case series	1 F 1 M	22, 41	1 Pfizer 1 Moderna	Hypothyroidism, rheumatoid arthritis, Raynaud syndrome	*After 1st dose*: Annular plaques (2)	100% (2/2)	100% (2/2) exacerbation of SCLE
Oniszczuk et al. 2021; France	Case report	1 F	34	1 Pfizer	Raynaud phenomenon	*After 1st dose*: Sclerotic skin (1)	100% (1/1)	100% (1/1) exacerbation of dcSSc
Patil et al. 2021; India	Case report	1 F	22	1 AstraZeneca	None	*After 2nd dose*: Unspecified rash (1), petechiae (1)	100% (1/1)	100% (1/1) new onset SLE
Raviv et al. 2022; Israel	Case report	1 M	24	1 Pfizer	None	*After 1st dose*: Erythematous plaques (1)	100% (1/1)	100% (1/1) new onset SLE
Sprow et al. 2022; US	Case series	2 F	60, 72	1 Pfizer 1 Moderna	Discoid lupus, morphea	*After 1st dose*: Sclerotic skin (1), hyperpigmentation (1) *After 2nd dose*: Sclerotic skin (1)	100% (2/2)	100% (2/2) new onset scleroderma-myositis and new onset eosinophilic fasciitis
Sugimoto et al. 2022; Japan	Case report	1 F	41	1 Moderna	SLE	*After 1st dose*: Malar rash (1) *After 2nd dose*: Skin ulceration (1)	100% (1/1)	100% (1/1) exacerbation of SLE
Vutipongsatorn et al. 2022; UK	Case report	1 F	55	1 Pfizer	Type 2 diabetes mellitus	*After 1st dose*: Pink-violaceous erythema (1)	100% (1/1)	100% (1/1) new onset of DM
Wu et al. 2022; US	Case report	1 F	77	1 Pfizer	None	*After 1st dose*: Pink-violaceous erythema (1)	100% (1/1)	100% (1/1) new onset of DM
Yoshida et al. 2022; Japan	Case series	2 F	81, 87	2 Pfizer	Not reported	*After 1st dose*: Heliotrope rash (2)	100% (2/2)	100% (2/2) new onset of DM
Yuki et al. 2021; Brazil	Clinical trial	208 F 24 M	Median: 40.5 (18–73)	223 Sinovac	SLE	*After 1st dose*: Unspecified rash (1) *After 2nd dose*: Unspecified rash (5)	*After 1st dose*: 0.43% (1/232) *After 2nd dose*: 2.16% (5/232)	100% (6/6) exacerbations of SLE
Zavala-Flores et al. 2021; Peru	Cohort	94 F 6 M	Median: 35 (27.5–49)	100 Pfizer	SLE	*After 1st dose*: None *After 2nd dose*: Malar rash (4)	*After 1st dose*: 0% (0/100) *After 2nd dose*: 4.44% (4/90)	100% (4/4) exacerbations of SLE
Zengarini et al. 2022; Italy	Case report	1 F	30	1 Pfizer	Primary biliary cholangitis	*After 2nd dose*: Erythematous papules (1)	100% (1/1)	100% (1/1) new onset of SCLE

F, female; M, male; dcSSc, diffuse cutaneous systemic sclerosis; DM, dermatomyositis; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

[a]For studies with >2 patients, the age of all individuals within the study was reported as "*mean ± standard deviation*" or "*median (interquartile range)*".

Table 2 The timing to onset of symptoms after COVID-19 vaccination and the most common connective tissue diseases and cutaneous symptoms reported

Timing to onset of symptoms (n = 81)	
After 1st COVID-19 vaccine	55.6% (45/81)
After 2nd COVID-19 vaccine	44.4% (36/81)
Mean ± SD latency time between vaccination and onset of symptoms	10.7 ± 9.4 days
Connective tissue diseases and symptoms[a] (n = 93)	
Autoimmune sclerosing diseases (n = 48)	
Raynaud's phenomenon	39.6% (19/48)
Sclerotic skin	10.4% (4/48)
Skin ulceration	4.2% (2/48)
Erythematous violaceous plaque	2.1% (1/48)
Hyperpigmentation	2.1% (1/48)
Unspecified rash	47.9% (23/48)
Lupus (n = 39)	
Malar rash	17.9% (6/39)
Erythematous papules/plaques	7.7% (6/39)
Annular plaques	10.3% (3/39)
Erythematous macules/patches	7.7% (3/39)
Skin ulceration	2.6% (1/39)
Hyperpigmentation	2.6% (1/39)
Eyelid edema	2.6% (1/39)
Unspecified rash	51.3% (20/39)
Dermatomyositis (n = 6)	
Pink-violaceous erythema	66.7% (5/6)
Heliotrope rash	50% (3/6)
Crusted lesions	16.7% (1/6)

[a]Cutaneous symptoms were sorted into one or more categories.

vaccine. Skin symptoms occurred at an average of 10.7 ± 9.4 days post-vaccination.

We believe that the benefits of the COVID-19 vaccination outweigh potential risks in most individuals given the low incidence of adverse effects after vaccination. One review, which found that only a small percentage of patients developed autoimmunity after COVID-19 vaccination, suggested that autoimmunity may occur in genetically predisposed patients.[2] Based on our findings, patients with pre-existing connective tissue diseases may benefit from counseling before vaccination about the risk of relapse or exacerbation, whereas those without pre-existing connective tissue conditions appear less likely to develop cutaneous symptoms after vaccination.

The relationship between COVID-19 vaccination and autoimmunity remains unclear, but several potential mechanisms have been described. COVID-19 vaccination may lead to development of autoantibodies due to cross-reactivity of SARS-CoV-2 proteins and tissue antigens.[2,3] One in vitro study found moderate-to-severe cross-reactivity of SARS-CoV-2 proteins to 21 of 50 human tissue antigens.[4] Moreover, mRNA-containing lipid nanoparticles (LNPs), found in vaccines manufactured by Pfizer and Moderna, may trigger autoimmunity by upregulating production of pro-inflammatory cytokines and chemokines.[2] Vaccine adjuvants may activate the NLR pyrin domain containing 3 (NLRP3) inflammasome, an intracellular receptor implicated in the pathogenesis of systemic lupus erythematosus, systemic sclerosis, and other autoimmune diseases.[5]

Limitations of our study include reliance on self-reported data (in two cross-sectional studies), lack of comprehensive data, and small sample sizes. We recognize the overwhelming benefits of COVID-19 vaccination in reducing COVID-19 morbidity and mortality. However, we encourage further studies to better characterize the relationship between COVID-19 vaccination and autoimmune cutaneous symptoms.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Concerning the assessment of outcomes in the treatment of actinic cheilitis. Comment on: "Cheilitis Actinica: topical treatment with 3.75% imiquimod"

Dear Editor,

Actinic cheilitis (AC) is a subject of critical importance due to the high risk of malignization; however, systematic longitudinal large-sample controlled trials on AC treatment are scarce, leaving its treatment hierarchy undefined.[1] The search for highly