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BRIEF REPORT

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Temporal association between COVID-19 vaccination and Raynaud's phenomenon: A case series

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ABSTRACT

COVID-19 vaccine–related adverse events are mostly minor to moderate, and serious events are rare. Single cases of Raynaud's phenomenon (RP) in temporal proximity to COVID-19 vaccination have been reported. Demographic data, medical history, and detailed information regarding vaccination status and RP characteristics were obtained from patients with confirmed RP after COVID-19 vaccination. Fifteen participants reported the initial manifestation of RP, which occurred in 40% after the first, in 33% after the second, and in 27% after the third vaccination. RP development and occurrence of episodes were not linked to any specific vaccine type. New onset of disease was observed in 40% of the vaccinees after BNT162b2, in 33% after mRNA-1273, and in 27% after ChAdOx1 vaccination. Three out of four participants with preexisting RP prior to COVID-19 vaccination reported aggravation in frequency and intensity after immunization. Although COVID-19 vaccination is pivotal in controlling the pandemic, the observed temporal association between vaccine administration and RP occurrence warrants global activities to support pharmacovigilance for the detection of adverse reactions, one of which may include RP.

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Introduction

As of March 8, 2023, 13.33 billion COVID-19 vaccine doses have been administered globally, allowing for 69.7% of the world's population to have received at least one vaccination.[1,2] Active drug safety surveillance programs have led to numerous reports on vaccine-induced adverse effects of mostly mild-to-moderate severity. Rarely, severe adverse events including anaphylaxis, thrombosis with thrombocytopenia syndrome, myocarditis, and Guillain–Barré syndrome have been reported.[3] In 2021, we reported the case of a healthy woman who developed Raynaud's phenomenon (RP) shortly after COVID-19 vaccination.[4] RP, an episodic, vasospastic disorder of the skin's small muscular arteries, usually manifests with a triphasic attack of pallor, cyanosis, and rubor, particularly on fingers and toes.[5] The most common primary form is idiopathic, and the secondary form is associated with underlying autoimmune, inflammatory, hematopoietic, or vascular diseases, certain medications, or vibratory trauma.[5,6]

Methods

This study was instigated by several patients from different countries who had read the case report[4] and reported the new onset or aggravation of RP after COVID-19 vaccination. Approval was obtained from the ethics committee of the Medical University of Vienna, Austria (EK 1152/2022). All participants gave written informed consent, and the study was conducted at the Department of Dermatology, Medical University of Vienna, Austria, in accordance with the principles stated in the Declaration of Helsinki, between January 1 and June 30, 2022.

A total of 19 adults with confirmed RP after COVID-19 vaccination were included in this study. Twelve participants resided in countries outside Austria, 6 participants were recruited from the Department of Angiology, Medical University of Vienna, Austria, and follow-up data from the initial patient[4] were obtained. The investigated vaccines included the mRNA-based vaccines BNT162b2 (C) ("Comirnaty;" Pfizer-BioNTech, USA/Germany) and mRNA-1273 (S) ("Spikevax;" Moderna Inc., USA) and the adenovirus vector-based vaccine ChAdOx1 (V) ("Vaxzevria;" AstraZeneca, UK/Sweden). Demographic parameters (age, sex, and country of residence), medical history (comorbidities, previous COVID-19 infection and surgeries, body mass index), and detailed information regarding COVID-19 vaccination status and RP characteristics (symptoms, localization, time between vaccination and occurrence of RP, number of attacks) were obtained via questionnaire. Additionally, 10 participants provided information on hematologic, biochemical, coagulation, and immunological blood parameters, and capillary microscopy and optical pulse oscillography results were available for five and six participants, respectively.

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Results

Demographic characteristics of the study participants

A total of 19 patients with RP (Figure 1) were included, of whom 79% (15/19) reported the development of RP after and 21% (4/19) a history of preexisting RP prior to COVID-19 vaccination. The demographic data are summarized in Table 1.

Initial manifestation of RP after COVID-19 vaccination

The new onset of RP after COVID-19 vaccination occurred in 15 participants (Patients 1–15). Sixty percent (9/15) were female and 40% (6/15) were male, with a median (range) age of 42 (31–63) years. In total, 42 vaccine doses were administered consisting of 23 doses of C, 11 doses of S, and 8 of V (Table 2). 27% (4/15)

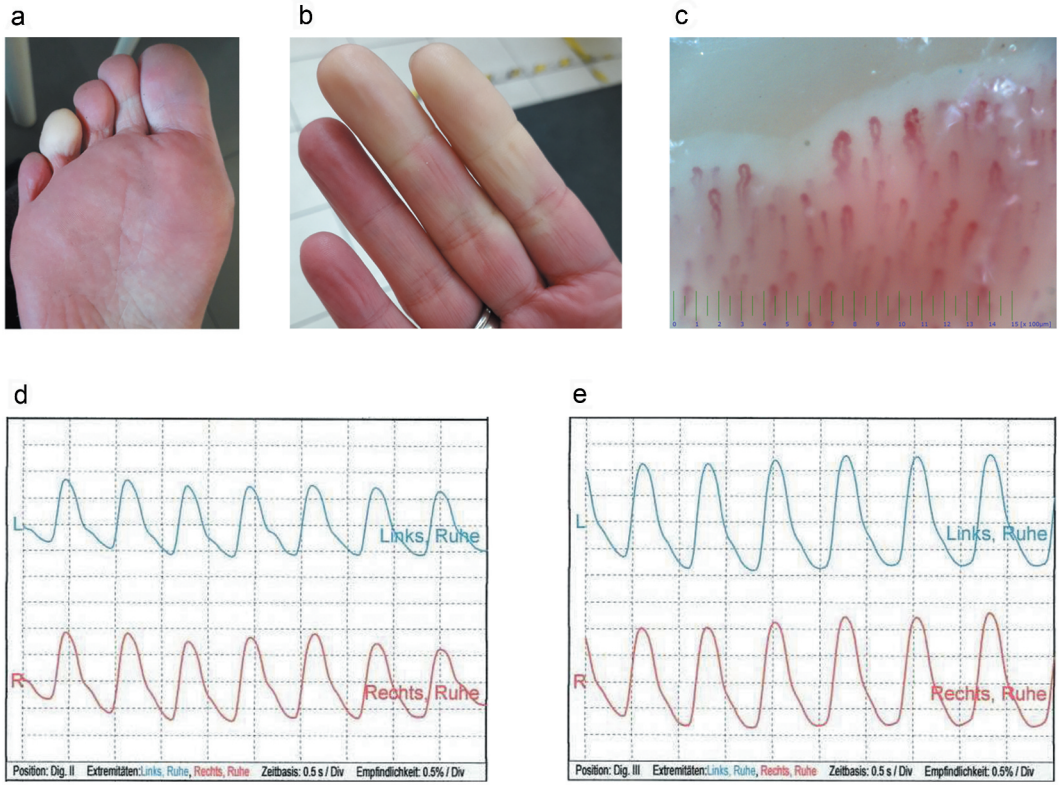

Figure 1. Representative female participant with new onset of Raynaud´s phenomenon after COVID-19 vaccination. a. Well-demarcated, white-pale, cold fourth toe of the right foot. b. Affected index and third finger of the right hand with sharp demarcation of skin pallor. c. Nailfold capillaroscopic image of the affected third finger of the right hand, showing dilatation, torsion and reduced capillary density, but lack of megacapillaries. d and e. Optical pulse oscillograms of the index (d) and the third finger (e) of the affected right hand (red) and the unaffected left hand (blue-green) revealing regular oscillations.

Table 1. Demographic data of 19 individuals with Raynaud's phenomenon.

Patient number	Age, years	Sex	Localization	RP prior to COVID-19 vaccination	COVID-19 infection before onset of RP	Possible predisposing factors for RP	Country of residence
1	31	F	H, T	No	No	No	U.S.A.
2	44	F	H	No	No	Former smoker	U.S.A.
3	63	M	H, T	No	No	History of frostbite (hands) and surgery (arms, foot)	U.S.A.
4	63	M	H	No	No	Beta blockers	U.S.A.
5	32	F	H, T	No	Yes	No	Argentina
6	42	F	H, T	No	No	ANAs	Austria
7	47	F	H	No	Yes	Goiter	U.K.
8	31	F	H	No	No	Hashimoto's disease	Poland
9	31	F	H	No	No	No	Austria
10	41	F	H, T	No	No	Former smoker, beta blockers, ANAs	Austria
11	39	M	H	No	No	No	U.S.A.
12	62	M	H	No	No	History of frostbite (hand)	Switzerland
13	54	M	H	No	No	No	U.S.A.
14	31	M	H	No	Yes	Hypothyroidism, anti-cardiolipin antibodies	Austria
15	52	F	H, T	No	No	ANAs	Austria
16	60	F	H	Yes	No	Former smoker, low BMI	U.K.
17	25	F	T	Yes	No	Smoker, Hashimoto's disease	Austria
18	56	F	H, T	Yes	No	Strumectomy, beta blockers, triptans	Austria
19	48	F	H, T	Yes	No	No	U.S.A.

RP: Raynaud's Phenomenon, F: female, M: male, H: hands, T: toes, ANAs: antinuclear antibodies, BMI: body mass index.

Table 2. Main characteristics of 15 individuals with new-onset Raynaud's phenomenon.

	RP after 1st vaccination				RP after 2nd vaccination				RP after 3rd vaccination			
Patient No.	VAX	RP	Days to onset	Number of attacks	VAX	RP	Days to onset	Number of attacks	VAX	RP	Days to onset	Number of attacks
1	S	No	NA	NA	S	Yes	17	>50	S	Yes	2	>50
2	S	No	NA	NA	S	Yes	14	31–50	No	NA	NA	NA
3	C	No	NA	NA	C	Yes	180	?	No	NA	NA	NA
4[a]	C	No	NA	NA	C	No	NA	NA	C	Yes	112	1–5
5	V	Yes	14	1–5	V	Yes	7	16–20	S	Yes	7	1–5
6	V	No	NA	NA	V	Yes	126	>50	C	No	NA	NA
7	S	Yes	21	1–5	S	No	NA	NA	C	Yes	35	1–5
8	C	Yes	14	1–5	C	No	NA	NA	C	Yes	4	1–5
9	V	Yes	7–14	6–10	V	Yes	?	6–10	C	Yes	?	6–10
10	C	No	NA	NA	C	No	NA	NA	C	Yes	35	21–30
11	C	No	NA	NA	C	No	NA	NA	S	Yes	1	1–5
12	C	No	NA	NA	C	Yes	3	>50	No	NA	NA	NA
13	S	Yes	>1	6–10	S	Yes	>1	31–50	No	NA	NA	NA
14	C	No	NA	NA	C	No	NA	NA	C	Yes	30–60	1–5
15	V	Yes	5	11–15	V	Yes	56	11–15	C	Yes	<1	21–30

RP: Raynaud's Phenomenon, VAX: COVID-19 vaccine, NA: not applicable, S: mRNA-1273, C: BNT162b2, V: ChAdOx1, ?: unknown.
[a]The details of Raynaud's Phenomenon after the fourth vaccination are not listed, as the only participant (Patient 4), who had received a fourth dose, did not report the occurrence of attacks at this time point.

of the participants received two, 67% (10/15) three, and 7% (1/15) four immunization doses.

Disease development did not depend upon the number of vaccine doses received, as the initial manifestation of RP was observed in 40% (6/15) after the first, in 33% (5/15) after the second, and in 27% (4/15) after the third immunization. RP attacks continued to be present after subsequent immunizations in the majority of the afflicted participants. However, Patients 7 and 8 reported RP attacks after the first and third, but not after the second vaccination, and in Patients 4 and 6, RP was not observed after booster vaccinations. The typical RP symptoms occurred after 3–21 (median 12) days after the first, 3–180 (median 16) days after the second and 0–112 (median 7) days after the third vaccination dose, and the reported numbers of attacks ranged from 1 to 15 after the first, from 31 to more than 50 after the second, and from 1 to 30 episodes after the third immunization. New onset of disease was observed in 40% (6/15) of the participants after C, in 33% (5/15) after S, and in 27% (4/15) after V vaccine administration. Evaluation of all, primary and booster, vaccinations administered to the participants revealed that RP episodes had been reported after 46% (10/22) of C, after 73% (8/11) of S, and after 88% (7/8) of V immunizations. In most of the participants (67%, 10/15), predisposing factors for RP[6] were identified, such as detectable antinuclear (20%, 3/15) or anti-cardiolipin antibodies (7%, 1/15), thyroid disorders (20%, 3/15), smoking (13%, 2/15), concomitant use of beta-blockers (13%, 2/15), or antecedent frostbites (13%, 2/15). Otherwise, timely matching blood results did not reveal grossly abnormal values.

Exacerbation of preexisting RP following COVID-19 vaccination

Preexisting RP was reported by four out of the 19 participants (Patients 16–19). All (4/4) were females with a median age of 52 years, range 25–60 years. In 75% (3/4) of them, predisposing factors for RP were present and comprised smoking, thyroid disorders, a low body mass index, and the use of certain medications (Table 1). Notably, none suffered from a concurrent autoimmune or connective tissue disease linked to RP, such as systemic lupus erythematosus or scleroderma. Aggravation in frequency and intensity of the RP attacks after COVID-19 vaccination, including the involvement of previously unaffected fingers (Patient 16), was reported by 75% (3/4) after homologous and heterologous vaccinations with C, S, and V vaccines.

Discussion

To date, only isolated cases of RP in temporal proximity to COVID-19 vaccination have been published.[4,7,8] In this case series, 19 individuals with RP occurring after COVID-19 vaccination, of whom 15 negated previous RP attacks, are presented. This case series does not infer a causal relationship between vaccination and the occurrence of RP, however, the temporal relationship seems unsettling. The occurrence of RP was additionally reported after human papillomavirus, hepatitis B, and diphtheria-tetanus vaccination.[9–13]

The current COVID-19 vaccines were designed to direct human cells to produce the SARS-CoV-2 spike protein, which mediates entry of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into the host cells via its receptor, angiotensin-converting enzyme 2 (ACE2). The introduction of the viral protein into the host's organism in turn stimulates production of neutralizing antibodies and T-cell-mediated immune responses in vaccinated subjects. Despite the indisputable, beneficial effects of COVID-19 vaccination, the presence of the spike protein could nevertheless account for some undesired adverse effects, including RP, in selected individuals. In this regard, circulating spike protein was detected in the blood, and deposition of the spike protein was shown in the microvasculature of the skin of COVID-19 vaccine recipients.[14,15] Different scenarios are possible how the vaccine's spike protein might promote RP. First, the spike protein has been shown to be able to induce a hyperinflammatory state including the release of a pro-inflammatory cytokine storm, subsequently causing immune cells to target and damage endothelium, neurons, perivascular cells, or other parts of the skin's neurovascular system.[16,17] Second, the spike protein

per se was shown to be able to impair endothelial cell function, which might favor vasoconstrictory events, as observed in RP.[18–20] Third, activation of the renin angiotensin system (RAS), caused by the interaction of the spike protein with the ACE2 receptor, could lead to an increase in the sympathetic nervous system tone and subsequent dysregulation of acral perfusion.[21] Fourth, the spike protein was shown to influence hemostasis by supporting a procoagulant state.[20] Finally, the spike protein might induce cross-reactive anti-viral antibodies via molecular mimicry[16,22] that in turn could activate autoimmunological processes against endothelial and nerve cells or favor platelet activation. Although the exact pathogenic mechanisms are not yet known, each aforementioned scenario or a combination thereof raises the possibility that the spike protein may act as an additional trigger in the development of RP.

Primary RP, however, is not a rare disease. An overall pooled prevalence of primary RP in the general population of 4.85% with a mean annual incidence of 0.25% was reported in a meta-analysis comprising more than 33,000 participants, and female gender, a family history of primary RP, migraine, and smoking were associated with disease development.[23] Given the high incidence of predisposing factors in our cohort, it is conceivable that some of our participants with new-onset RP could have acquired disease at some point during their lifetime, regardless of COVID-19 vaccination and therefore disease development after vaccination could merely be coincidental. Future, particularly mechanistic as well as large scale, studies are needed to elucidate a potential association between COVID-19 vaccination and RP and to investigate whether COVID-19 vaccination might provide an additional stimulus for an earlier manifestation of RP in cases with predisposition.

The therapeutic options in patients with primary RP do not differ between COVID-19 vaccinated and unvaccinated individuals and include lifestyle changes, such as avoidance of cold exposure and cessation of smoking, and pharmacologic management with calcium channel blockers. COVID-19 vaccination should still be performed to obtain protection against COVID-19 disease, including the risk of severe illness and death.

This study is limited by the small sample size, lack of a control group, and its questionnaire-based design, the latter of which was necessary due to the transnational inclusion of participants. Furthermore, a selection bias may exist as the majority of the study participants consisted of individuals who had read the initial case report.[4] However, this case series was not intended to compare the effect of different vaccine types or brands, as valid statistical analyses were hampered by the limited sample size and the binary nature of the findings.

Given the high number of administered COVID-19 vaccines and the recent authorization of adapted vaccine formulations targeting new SARS-CoV-2 subvariants,[24] immunization as part of managing the COVID-19 pandemic will remain of pivotal importance. Thus, physicians and patients need to stay alert to adverse effects, one of which may include RP. Global collaborations and support of the pharmacovigilance systems need to be continued and strengthened to ensure the rapid identification and efficient reduction of potential safety risks in order to protect public health and to keep the public's trust in vaccination.

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