The Journal of Rheumatology 2022;xx:xxxx
doi:10.3899/jrheum.220487
First Release August 1 2022

The Journal of Rheumatology

Letter

Chilblains After SARS-CoV-2 Vaccination: Coincidence or Real Association?

To the Editor:

We read with great interest the article of Meara et al[1] in your journal describing a case of chilblain-like lesions after vaccination against SARS-CoV-2. Since the start of the coronavirus disease 2019 (COVID-19) pandemic, millions of vaccine doses have been administered and their safety has been generally confirmed. However, case reports and small case series indicate that vaccination against COVID-19 might be associated with autoimmune adverse reactions,[2] although a causal relationship cannot be easily established. Along these lines, a few cases of chilblains development after anti-SARS-CoV-2 vaccination have been reported.[1,3,4] Interestingly, COVID-19 itself can be also complicated by chilblain-like rash appearance.[5]

Over the last few months, an unusual number of patients presented in our outpatient rheumatology clinics complaining of chilblains. This observation, in relation to the above-mentioned evidence, prompted us to report these findings, in which we speculate that these lesions could be related to vaccination against

Table. Characteristics of patients that developed chilblain-like lesions after anti-SARS-CoV-2 vaccination.

Sex	Age, Yrs	Smoking	History of ARD	ARD	Chilblains Ever	Last Vaccination Date, Mo/Yr	Vaccine Type/Dose	Symptoms Onset, Mo/Yr	Treatment	Symptoms	Outcome
F	42	Never	No	–	No	10/2021	BNT162b2/2nd	1/2022	None	cll, PIP arthritis	Resolved after 60 days
F	24	Never	No	–	No	9/2021	BNT162b2/3rd	12/2021	None	cll, PIP arthritis	Resolved after 10 days
F	15	Never	No	–	No	12/2021	BNT162b2/3rd	1/2022	Topical GC	cll, PIP arthritis	Resolved after 15 days
F	25	Never	No	–	No	10/2021	BNT162b2/2nd	1/2022	Topical GC	cll, dactylitis	Resolved after 20 days
F	32	Current	No	–	No	11/2021	BNT162b2/3rd	2/2022	None	cll, PIP arthritis	Resolved after 60 days
F	32	Never	No	–	No	7/2021	BNT162b2/2nd	1/2022	None	cll, dactylitis	Resolved after 20 days
F	16	Never	No	–	No	9/2021	BNT162b2/2nd	2/2022	None	cll, dactylitis	Resolved after 25 days
F	41	Never	No	–	No	7/2021	BNT162b2/2nd	10/2021	None	cll, dactylitis	Resolved after 20 days
F	53	Current	No	–	No	8/2021	BNT162b2/2nd	11/2021	None	cll, dactylitis	Resolved after 20 days
M	32	Never	No	–	No	3/2021	BNT162b2/2nd	5/2021	Oral GC	cll, PIP arthritis, dactylitis	Relapsing/remitting[a]
F	56	Never	No	–	No	7/2021	BNT162b2/2nd	12/2021	None	cll, dactylitis	Resolved after 15 days
F	25	Never	Yes	UCTD	No	1/2022	BNT162b2/3rd	1/2022	None	cll, PIP arthritis	Persistent[b]
F	42	Current	No	–	No	7/2021	mRNA-1273/2nd	10/2021	Smoking cessation	cll, dactylitis	Persistent
F	67	Current	Yes	lcSSc	No	1/2022	BNT162b2/1st	1/2022	None	cll, dactylitis	Resolved after 7 days
F	39	Current	No	–	Yes	12/2021	BNT162b2/3rd	2/2022	Topical GC	cll, dactylitis	Resolved after 40 days
F	36	Current	No	–	Yes	12/2021	BNT162b2/3rd[c]	1/2022	Topical GC	cll, dactylitis	Resolved after 15 days
F	32	Never	No	–	No	11/2021	BNT162b2/3rd	3/2022	Topical GC, NSAIDs, Oral GC	cll, dactylitis	Relapsing/remitting[a]
F	56	Never	No	–	No	10/2021	BNT162b2/3rd	11/2021	None	cll	Persistent
F	31	Never	No	–	No	7/2021	BNT162b2/2nd	12/2021	Topical GC	periodic (every 7 days) dactylitis, pruritus	Resolved after 3 months
F	22	Never	No	–	No	11/2021	BNT162b2/2nd	2/2022	None	cll	Resolved after 15 days
M	71	No/Ex	No	–	No	11/2021	BNT162b2/3rd[d]	3/2022	IM GC	cll, PIP arthritis, pruritus	Ongoing[e]
F	57	No/Ex	No	–	No	12/2021	BNT162b2/3rd	1/2022	None	cll, PIP arthritis, pruritus	Resolved after 30 days
F	59	Never	Yes	IIM	No	12/2021	BNT162b2/3rd	12/2021	IM GC	cll, PIP arthritis	Resolved after 4 days
F	37	Current	No	–	Yes	7/2021	BNT162b2/2nd	10/2021	None	cll, PIP arthritis, dactylitis	Persistent
M	53	Current	No	–	Yes	7/2021	mRNA-1273/3rd	12/2021	None	cll, PIP arthritis, dactylitis	Resolved after 120 days

[a] Relapsing/remitting: episodes of relapses/remission. [b] Persistent: defined as lesions still active after 3 months. [c] This patient received ChAdOx1 nCoV-19/AZD1222 (1st and 2nd dose). [d] This patient received mRNA-1273 (1st and 2nd dose). [e] Improved but symptomatology is ongoing after 30 days. ARD: autoimmune rheumatic disease; cll: chilblain-like lesions; GC: glucocorticoid; IIM: idiopathic inflammatory myopathy; IM: intramuscular; lcSSc: limited cutaneous systemic sclerosis; NSAID: nonsteroidal antiinflammatory drug; PIP: proximal interphalangeal joint; UCTD: undifferentiated connective tissue disease.

SARS-CoV-2. In total, out of the 359 patients attending for the first time our outpatient rheumatology clinics between October 2021 and February 2022, the presenting symptom in 25 (7.0%) patients was chilblain-like lesions (ie, erythematous to violaceous macules, papules, plaques, or nodules), accompanied or not by dactylitis and/or arthritis (Table). The majority (22/25, 88%) were female and their mean age was 39.25 (SD 15.6) years. Three patients had a history of autoimmune rheumatic disease (ARD) and 4 also had a history of chilblains. None of them had a history of infection with SARS-CoV-2.

The mean time to chilblain appearance after last vaccine dose was 2.88 (SD 1.53) months, either after the first (n = 1), second (n = 12), or third (n = 12) dose with mRNA vaccines. No treatment was given in 15/25 patients. Ten patients received glucocorticoids (GCs; 6 topical, 2 oral, 2 intramuscular). Most cases followed a benign course, resolving completely in 18/25 (72%) patients within 2 months (mean 32.6 [SD 31.1] days) from onset. However, 4 patients who received no treatment and 1 who received intramuscular GCs experienced persistent (lesions still active after 3 months) and ongoing (improvement but symptomatology is ongoing after 30 days) chilblains, respectively; 2 patients who received oral or topical GCs and nonsteroidal antiinflammatory drugs (Table) exhibited relapsing/remitting symptoms.

Several skin reactions, including injection-site reactions, urticaria, erythema multiforme-like, pityriasis rosea–like lesions, and leukocytoclastic vasculitis have been described after COVID-19 vaccination,[6] whereas vaccine-related chilblain-like rash is also increasingly recognized.[1,4,6] Chilblains are erythematous or violaceous skin lesions that develop in extremities after exposure to cold. These lesions are often painful,[1,4] making it difficult to differentiate them from frank arthritis.

The possible pathogenetic mechanisms linking chilblains with COVID-19 vaccines are unknown; however, endothelial dysfunction and immune activation, especially type I interferon (IFN-I) response, might be involved.[3] Of note, in a recent post vaccine pernio-like case by Lesort et al, blood IFN signature was enhanced.[4] A robust IFN-I pathway activation has been reported in mild COVID-19 infection and was associated with chilblain-like lesion development,[7] while strong IFN-I response has been observed shortly after vaccination with mRNA anti–SARS-CoV-2 vaccination.[8] Of note, all cases reported to date occurred after vaccination with mRNA vaccines.[1,4]

Similar to the published case reports so far, most of the patients in our study were women and developed chilblains shortly after vaccination.[1,4] Also, in line with other post vaccine autoimmune events, the course of symptoms for most individuals who developed chilblains was benign and self-limited.[2,6] Considering that most of our cases were reported during the winter period, it is plausible that exposure to cold and vaccination against SARS-CoV-2 might have acted synergistically in the development of chilblains.

Our study has certain limitations. First, we cannot prove a causal relationship between SARS-CoV-2 vaccination and chilblains. However, the self-limiting nature of symptoms in addition to the temporal proximity between the events supports our argument. Importantly, in examining the frequency of chilblain-like lesions as a presenting symptom during the same time period 1 year ago (October 2020 to February 2021), we found only 2/154 (1.3%, P = 0.008 vs 2021–2022) patients fulfilling these criteria. Notably, vaccination in our country for the general population started in March 2021. Second, 3 of our patients had an underlying rheumatic disease, so we cannot exclude that this might have contributed to some extent in the appearance of chilblains. Of note, in 2 of these individuals, chilblains resolved without treatment after 4 to 7 days. In the rest of the patients, antinuclear and extracted nuclear autoantibodies as well as rheumatoid factor were negative, whereas complement levels were within normal range.

In conclusion, we report an increased frequency of new chilblains as a presenting manifestation in a rheumatology outpatient setting during the last 5 months. We speculate that this may be related to vaccination against SARS-CoV-2. Rheumatologists should be alert for this condition, as the clinical picture can easily resemble symptoms seen in ARDs.

Anastasios Karamanakos[1], MD
Gerasimos Evangelatos[1], MD
Maria Pappa[1], MD, PhD
Kalliopi Fragiadaki[1], MD, PhD
Antonis Fanouriakis[1], MD, Assistant Professor
George E. Fragoulis[1], MD, PhD
[1]Joint Academic Rheumatology Program, First Department of Propedeutic and Internal Medicine, National and Kapodistrian University of Athens, Athens, Greece.

The authors declare no conflicts of interest relevant to this article.

Address correspondence to Dr. G.E. Fragoulis, Joint Academic Rheumatology Program, First Department of Propedeutic Internal Medicine, Laiko Hospital, School of Medicine, National and Kapodistrian University of Athens, Agiou Thoma 17 Goudi, 11527, Athens, Greece. Email: geofragoul@yahoo.gr.

REFERENCES

1. Meara AS, Silkowski M, Quin K, Jarjour W. A case of chilblains-like lesions post SARS-CoV-2 vaccine? J Rheumatol 2021;48:1754.
2. Ishay Y, Kenig A, Tsemach-Toren T, et al. Autoimmune phenomena following SARS-CoV-2 vaccination. Int Immunopharmacol 2021;99:107970.
3. Qiao JW, Dan Y, Wolf ME, et al. Post-vaccination COVID toes (chilblains) exacerbated by rituximab infusion suggests interferon activation as mechanism. Mil Med 2021 Jul 23 (Epub ahead of print).
4. Lesort C, Kanitakis J, Donzier L, Jullien D. Chilblain-like lesions after BNT162b2 mRNA COVID-19 vaccine: a case report suggesting that 'COVID toes' are due to the immune reaction to SARS-CoV-2. J Eur Acad Dermatol Venereol 2021;35:e630-2.
5. Sun Q, Freeman EE. Chilblains and COVID-19–an update on the complexities of interpreting antibody test results, the role of interferon alpha, and COVID-19 vaccines. JAMA Dermatol 2022;158:217-8.
6. Gambichler T, Boms S, Susok L, et al. Cutaneous findings following COVID-19 vaccination: review of world literature and own experience. J Eur Acad Dermatol Venereol 2022;36:172-80.
7. Frumholtz L, Bouaziz JD, Battistella M, et al; Saint-Louis CORE (COvid REsearch). Type I interferon response and vascular alteration in chilblain-like lesions during the COVID-19 outbreak. Br J Dermatol 2021;185:1176-85.
8. Ntouros PA, Vlachogiannis NI, Pappa M, et al. Effective DNA damage response after acute but not chronic immune challenge: SARS-CoV-2 vaccine versus systemic lupus erythematosus. Clin Immunol 2021;229:108765.