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Association between COVID-19 and chilblains: a case–control study

Editor

Chilblain-like lesions (CLL) were described early on the coronavirus disease 2019 (COVID-19) pandemic as red-to-violet macules, plaques or nodules typically appearing at the distal aspects of toes.[1] Although increasing evidence suggests they are COVID-19-related,[2] it is not supported by analytic controlled studies.

In order to provide a greater degree of evidence on this issue, a unicentre-matched case–control study was designed. Participants were recruited between August and November 2020 at Ramon y Cajal University Hospital, Spain. Cases were defined by a new clinical diagnosis of chilblains (incident cases) and compared with controls. Each control was recruited in the same time frame and setting (concurrent sampling) and individually 1 : 1 matched by age and sex with cases. We calculated the sample size necessary to detect an OR = 4, which was 45 cases and 45 controls.[3] We administered structured questionnaires to cases and controls and examined them in the same manner. A validated serological test was done to assess the presence of antibodies.[4] A conditional logistic regression model was used to compare the prevalence of antibodies in both groups. All analyses were done with R software (version 4.0.3).

A total of 1347 patients were triaged to a dermatologist during the study period (Fig. 1), with 45 patients (3.34%) meeting the case definition and 522 patients meeting control definition. After 1 : 1 matching, baseline characteristics were well-balanced between cases and controls (Table 1). There were 5/45 (11.11%) positive patients among the controls and 17/45 (37.78%) positives among the cases. The odds ratio of a positive IgG against the receptor-binding domain of SARS-CoV-2 spike (S) protein was OR = 3.40 (95% CI, 1.25–9.22; $P = 0.0162$) in cases compared with controls. None of the cases required hospital admission.

There has been a wide controversy about the causal relation between COVID-19 and CLL as many patients do not show other symptoms and RT-PCR tests from skin specimens and even serological studies are often negative.[2,5–8] Attending to the results of our study, IgG antibodies against SARS-CoV-2 appear to be indeed a risk factor for CLL that overall occur in asymptomatic or mildly symptomatic patients, as none of the patients required hospitalization. It should be noted that more than half of the cases were seronegative. They could correspond to CLL not caused by the virus. Nevertheless, specific T cells have been detected in antibody-seronegative individuals with a history of asymptomatic and mild COVID-19.[9] Memory T-cell responses can occur in the absence or presence of circulating antibodies, consistent with a non-redundant role as key determinants of immune protection against COVID-19. T-cell responses are more common than circulating antibodies in mild and asymptomatic COVID-19 patients. Unfortunately, there are not T-cell activation tests available for clinical practice. We hypothesize that this skin manifestation could induce a weak antibody response but a robust cellular response, as it has been previously suggested triggering the release of IFN-I.[10] Our study has important limitations. The most obvious is the sample size. In addition, there may be a selection bias in patients who attend the emergency room for this reason leading to an overestimation of the seropositivity. We tried to overcome this limitation by being more restrictive in the case definition. Finally, histological confirmation was not required, but this allowed us not to further reduce the sample size. To conclude, we found a higher prevalence of IgG against SARS-CoV-2 in patients with CLL than in the control group, which suggests a causal relationship between both variables. However, further research is needed.

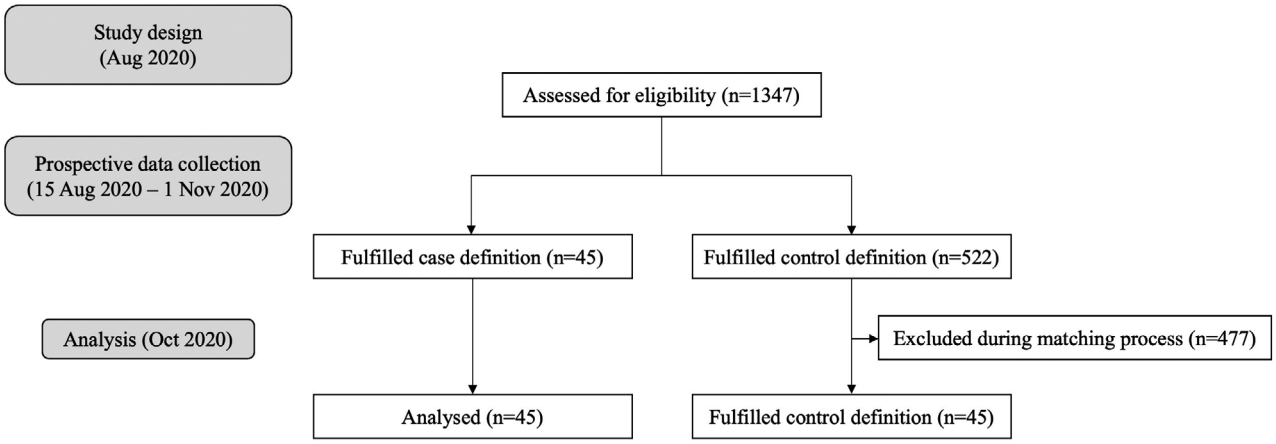

Figure 1 Study flow chart – Study flow chart in line with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.

Table 1 Baseline characteristics and statistical analysis

		Cases (n = 45)	Controls (n = 522)		
			Not matched (n = 477)	1:1 matched (n = 45)	
Age	Mean	30.73	42.28	30.77	
	Range	9–61	0–102	8–63	
Sex,	*n* (%)	37.7 female	50.9 female	37.7 female	
		62.3 male	49.1 male	62.3 male	
IgG positivity	*n* (%)	37.78	—	11.11	**OR = 3.40 (95% CI 1.25–9.22; *P* = 0.016)**†

CI, confidence interval; IgG, immunoglobulin G; *n*, number; OR, odds ratio.
†Obtained by conditional logistic regression analysis.

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Conflicts of interest
None declared.

IRB approval status
The study protocol was approved by the ethics committee (code 197/20). Written consent was obtained from the patients included in this study.

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Insights into Sars-CoV-2 vaccination in patients with chronic plaque psoriasis on systemic treatments

Dear Editor,

Two vaccines against COVID-19 have recently been approved by the FDA and EMA: BNT162b2 (BioNTech, Mainz, Germany and Pfizer, Pfizer Inc., New York, NY, USA) and mRNA-1273 (Moderna, Cambridge, MA, USA). Both vaccines utilize mRNA that enters the patient cell and uses host protein transcription pathways to express viral spike proteins which then stimulate a specific antibody and T-cell-mediated immune response.[1] They are both administered in two intramuscular doses: 3 weeks apart for BNT162b2, 4 weeks apart for mRNA-1273. Phase 3 trials showed high efficacy rate in protection against COVID-19[2,3] (95% for BNT162b2 and 94.1% for mRNA-1273) and no major safety concerns, with the most common adverse effects being injection site pain, headache, fever, fatigue, chills and myalgia.[2,3] As patients on immunosuppressive therapy were excluded from clinical trials, there are currently no data on the efficacy and safety of COVID-19 vaccines in those treated with conventional or biologic disease-modifying antirheumatic drugs (DMARDs). However, the COVID-19 vaccine will soon be available also for patients with psoriasis receiving systemic treatments and some considerations are needed in this regard. In terms of safety, both BNT162b2 and mRNA-1273 are expected to be safe in psoriatic patients on immunosuppressants given that they are not live vaccines as recently advised by the EADV Task Forces statements on COVID-19 Vaccination.[4] On the other hand, immunosuppressant treatment may theoretically reduce to some extent the efficacy of COVID-19 vaccines. Conventional and biologic DMARDs have diverse mechanisms of action, which account for their different degree of immunosuppression and/or immunomodulating properties, so that some agents may impair the build-up of an immune response against COVID-19 vaccine more than others. For example, the IL-17A inhibitor secukinumab was proved not to affect the humoral response to influenza vaccine of patients with psoriatic arthritis;[5] similarly, ixekizumab was shown not to suppress humoral immune response to tetanus and pneumococcal vaccination.[6] In a meta-analysis comparing the humoral response to influenza and pneumococcal vaccination in adult patients with rheumatoid arthritis, it was found that methotrexate but not TNF-α inhibitors exposure was associated with reduced 6B and 23F serotype pneumococcal vaccine response.[7] Another important issue is whether psoriatic patients should discontinue their immunosuppressive treatment before and after receiving the vaccine to optimize the efficacy of the vaccination. Of note, since Pfizer-BioNTech and Moderna vaccines are administered 3 and 4 weeks apart, respectively, the drug would need to be discontinued for several weeks and there would be a reasonable risk of psoriasis recurrence, also considering that the vaccination itself stimulate an IFN-γ and TNF-α release from Th1 cells.[8] Ultimately, the durability of the protection against SARS-CoV-2 following vaccination has not been fully elucidated.[2]

In conclusion, weighing the potential benefits and risks, we suggest providing SARS-CoV-2 vaccination for all psoriatic patients on immunosuppressant drugs, because, although they might show to be not as effective as in healthy subjects, they may still provide some degree of protection against COVID-19. In the current and dramatic pandemic, some degree of immunity is better than no degree of immunity at all. Psoriatic patients receiving COVID-19 vaccine and those who had COVID-19 infection should also be advised to continue to follow all current guidance to protect themselves and others, as recently recommended by the EADV task force on quality of life and patient-oriented outcome.[9]

Since there are case reports of immunosuppressed patients (but also immunocompetent individuals) developing COVID-19 reinfection, also psoriatic patients who already had COVID-19 infection should be considered for the vaccination.

Registries enrolling dermatological patients undergoing SARS-CoV-2 vaccination and proactive pharmacovigilance activities especially focusing on patients under immunosuppressants are urgently needed to guide clinical practice.[10]

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