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

Editor

Chilblain-like lesions (CLL) were described early on during 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.

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None.

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.

Table 1  Baseline characteristics and statistical analysis

|                   | Cases (n = 45) | Controls (n = 522) | 1:1 matched (n = 45) |
|-------------------|---------------|--------------------|---------------------|
|                   |               | Not matched (n = 477) |                     |
| 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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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. 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 (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. 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.

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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.

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