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COVID-19: Important Updates and Developments
Edited by Franco Rongioletti, MD, and Leonard J. Hoenig, MD

Chilblain-like lesions coinciding with the SARS-CoV-2 pandemic

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Abstract Chilblain-like lesions (CLL) coinciding with SARS-CoV-2 infection have been described. Previous systematic reviews suggest CLL are associated with younger age, an equal sex ratio, negative testing for SARS-CoV-2, and mild to no extracutaneous symptoms. A systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines on CLL coinciding with SARS-CoV-2 to clarify the demographic characteristics, clinical features, and resolution outcomes of these skin findings. One hundred twenty-eight studies, published between March 2020 and January 2022, met inclusion criteria and were summarized in this review, representing 4,982 cases of CLL. Available data showed a slight female predominance (55%, n = 2,471 of 4,472). The mean age was 25 years, ranging from 0 to 95 years. Most cases were not associated with extracutaneous signs and symptoms (63%, n = 1,649 of 2,636). Overall, 19% (n = 347 of 1,838) of patients tested positive for SARS-CoV-2 using polymerase chain reaction, serology, or tissue biopsy. Clinical course was generally benign with 80% (n = 979 of 1,224) of cases resolving and 47% (n = 204 of 432) resolving without receiving treatment. This review provides a comprehensive summary of CLL associated with SARS-CoV-2. CLL occurred at a mean age of 25 years with a slight female predominance. The majority had negative COVID-19 testing, no extracutaneous signs and symptoms, and resolution without recurrence.

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Introduction

COVID-19 is caused by SARS-CoV-2 and often presents with systemic, respiratory, gastrointestinal, and/or ear, nose, and throat signs and symptoms.1,2 Chilblain-like lesions (CLL), colloquially called “COVID toes,” are the most common cutaneous manifestation associated with COVID-19 (51.5%).3 CLL morphologically resemble chilblains: acral erythematosus to violaceous papules and plaques occasionally associated with pain and/or pruritus.4 Several reviews have summarized reports of CLL associated with SARS-CoV-2. CLL most often occur in younger individuals (mean age range, 17-21) and in an approximately
equal sex ratio.\textsuperscript{4,6} CLL are almost always located on the feet and more rarely on the hands.\textsuperscript{5,7} Prior systematic reviews reported that 36% to 47% of cases were not associated with extracutaneous signs and symptoms (ECS), particularly in patients under 20 years old.\textsuperscript{5,7} When ECS were present, they preceded CLL in 75% of cases, with an average latency period of 16 days.\textsuperscript{5} SARS-CoV-2 testing results reported an overall positivity rate of approximately 15%.\textsuperscript{4,5}

This contribution aims to provide an updated and comprehensive summary of CLL associated with SARS-CoV-2.

Methods

This systematic review was conducted in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Eligibility criteria for this review were established as follows (PICOS):

- Population: individuals of any age and sex with CLL coinciding with the SARS-CoV-2 pandemic.
- Intervention: any intervention including patients who were not treated and observed only.
- Comparator: any other treatment received; studies that reported on patients without a comparator group were also included.
- Outcomes: clinical characteristics of CLL, presence and characteristics of ECS, SARS-CoV-2 testing information, and clinical outcomes.
- Study design: any study design with primary data.

Literature search and screening

A literature search was conducted using the MEDLINE, Embase, and Scopus databases on January 8, 2022, using the search terms “COVID-19” or “coronavirus” or “2019-nCoV” or “SARS-CoV-2” and “chilblain-like” or “COVID toes” or “acral.” Title, abstract, and full-text screening was conducted in duplicate by two reviewers using Covidence online systematic review software (www.covidence.org). At the full-text screening stage, studies were excluded if they did not meet components of the PICOS eligibility criteria. Searches did not include any language or geographic restrictions. Level of evidence for included publications was determined using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence.\textsuperscript{7}

Data extraction was performed by two reviewers using a standardized extraction form that included study characteristics (publication year, country, study design, and sample size), patient characteristics (age and sex of participants), SARS-CoV-2 information (ECS, SARS-CoV-2 test result, type of testing), CLL information (location and morphology of lesions, temporal association of ECS, and onset of CLL), and outcomes (treatment, response outcome, follow-up time, recurrence). A pooled analysis was performed for studies with available outcome data.

Results

After title and abstract screening of 898 studies and full text review of 189 studies, 128 studies met inclusion criteria, representing 4,982 cases of CLL (Supplementary Figure 1). Studies were published between March 2020 and January 2022. In six contributions,\textsuperscript{8-13} researchers published a follow-up on cases reported in prior work. Thirty-five studies (27%) were based in Italy, 30 in Spain (23%), 21 in France (16%), and 19 in the United States (15%). According to available data, the majority of studies, 92% (n = 110 of 119) reported cases from the first wave of the pandemic (spring and summer 2020),\textsuperscript{14,15} while 3% (n = 4 of 119) reported cases from the second wave (fall and winter 2020-2021) and 1% (n = 1 of 119) from the third wave (mid-February 2021 to June 2021). The majority of studies were level of evidence 4 (66%, n = 85 of 128) and 5 (25%, n = 32 of 128) with the remaining studies level of evidence 3 (5%, n = 7 of 128) and 2 (3%, n = 4 of 128) (Supplementary Table 1).

Patient characteristics

Available data showed that 55% (n = 2,471 of 4,472) of cases were women. Mean age was 25 years, ranging from 0 to 95 years.

COVID-19 testing results

Overall, 19% (n = 347 of 1,838) of patients tested positive for SARS-CoV-2 using either polymerase chain reaction (PCR) of nasopharyngeal swab, serology (IgG, IgM, or IgA), PCR of biopsy specimen, or IgG against COVID-19 spike protein (Table 1). PCR test positivity rate was 9% (n = 132 of 1,503). Serologic antibody testing (IgG and IgM) positivity rate was 10% (n = 95 of 925). IgA, PCR of skin biopsy, and IgG against COVID-19 spike protein positivity rates were 15% (n = 30 of 204), 1% (n = 1 of 75), and 29% (n = 19 of 65), respectively.

Extracutaneous signs and symptoms

According to available data, 63% (n = 1,649 of 2,636) of cases were asymptomatic, whereas 37% (n = 987 of 2,636) had ECS (Table 1). Available data showed that 81% (n = 544 of 670) of ECS occurred prior to the onset of CLL (mean, 13 days prior; range, 1-270 days); 13% (n = 84 of 670) concomitantly with CLL; and 6% (n = 42 of 670) after the onset of CLL (mean, 7 days after; range, 1-19 days).

A subgroup analysis of patients who were SARS-CoV-2 positive revealed that ECS were reported in 72% (n = 90 of 125) of cases (Table 2). ECS occurred before CLL in 71% (n = 55 of 77) of cases (mean, 55 days prior; range, 2-270 days), concomitantly in 23% (n = 18 of 77), and after in 5% (n = 4 of 77) (Table 2).
### Table 1  Clinical characteristics, COVID-19 testing results, and outcomes of chilblain-like lesions coinciding with the COVID-19 pandemic.

| Clinical characteristics and outcomes | Cases |
|--------------------------------------|-------|
| **Patient characteristics (n = 4,982)** |       |
| Sex                                  |       |
| Boys and Men                         | 45% (n = 2,001 of 4,472) |
| Girls and Women                      | 55% (n = 2,471 of 4,472) |
| Age, y                               |       |
| Mean                                 | 25 (n = 2,326 of 4,982) |
| Range                                | 0-95 y |
| **CLL information**                  |       |
| Location*                            |       |
| Feet                                 | 90% (n = 2,195 of 2,429) |
| Hands                                | 18% (n = 431 of 2,429) |
| Other                                | 1% (n = 20 of 2,429) |
| **ECS Presence**                     |       |
| Yes                                  | 37% (n = 987 of 2,636) |
| No (asymptomatic)                    | 63% (n = 1,649 of 2,636) |
| **Timing of CLL**                    |       |
| After ECS                            | 81% (n = 544 of 670) |
| Mean (range), d                      | 13 (1-270) |
| Concomitant with ECS                 | 13% (n = 84 of 670) |
| Before ECS                           | 6% (n = 42 of 670) |
| Mean (range), d                      | 7 (1-19) |
| **SARS-CoV-2 infection information**|       |
| Positive SARS-CoV-2 test             | 19% (347 of 1,838) |
| Negative SARS-CoV-2 test             | 81% (1,491 of 1,838) |
| Positivity by type of test           |       |
| PCR                                  | 9% (n = 132 of 1,503) |
| Serologic test (IgG, IgM)            | 10% (n = 95 of 925) |
| IgA                                  | 15% (n = 30 of 204) |
| PCR on biopsy                        | 1% (n = 1 of 75) |
| IgG against spike protein            | 29% (n = 19 of 65) |
| **CLL outcomes**                     |       |
| Resolved                             | 80% (n = 979 of 1,224) |
| Mean response time                   | 16 d |
| Range                                | 1-252 d |
| No treatment                         | 47% (n = 204 of 432) |
| Treated                              | 53% (n = 228 of 432) |
| Systemic corticosteroids             | 8% (n = 10 of 126) |
| Topical corticosteroids              | 45% (n = 57 of 126) |
| Oral analgesia                       | 55% (n = 69 of 126) |
| Oral antihistamines                  | 19% (n = 24 of 126) |
| Systemic antimicrobials              | 6% (n = 7 of 126) |
| Topical antimicrobials               | 24% (n = 30 of 126) |
| Chloroquine, hydroxychloroquine      | 5% (n = 6 of 126) |
| Unresolved                           | 7% (n = 91 of 1,224) |
| Mean follow-up time                  | 64 d |
| Range                                | 9-495 d |
| Recurrent                            | 13% (n = 154 of 1,224) |
| Mean time to recurrence              | 71 d |
| Range                                | 5-196 d |

CLL, chilblain-like lesions; ECS, extracutaneous symptoms; PCR, polymerase chain reaction; n, number of patients; N, number of patients in which clinical characteristic or outcome reported.

Data are presented as % (n of N) unless otherwise indicated.

* Some patients had CLL reports on both hands and feet, for a total >100%.
Table 2  Clinical characteristics and outcomes of chilblain-like lesions coinciding with the COVID-19 pandemic in cases with positive COVID-19 testing.

| Clinical characteristics and outcomes | Cases |
|--------------------------------------|-------|
| **Patient characteristics (n = 188)** |       |
| Sex                                  |       |
| Boys and Men                         | 50% (n = 56 of 111) |
| Girls abd Women                      | 50% (n = 55 of 111) |
| Age, y                               |       |
| Mean                                 | 30 (n = 114 of 188) |
| Range                                | 7-80 y |
| **CLL information**                 |       |
| **Location**                         |       |
| Feet                                 | 86% (n = 83 of 96) |
| Hands                                | 23% (n = 22 of 96) |
| Other                                | 4% (n = 4 of 96) |
| **ECS Presence**                     |       |
| Yes                                  | 72% (n = 90 of 125) |
| No (asymptomatic)                    | 28% (n = 35 of 125) |
| **Timing of CLL**                    |       |
| CLL occurred after ECS               | 71% (n = 55 of 77) |
| Mean days after ECS                  | 55 d |
| Range                                | 2-270 d |
| Concomitant with ECS                 | 23% (n = 18 of 77) |
| CLL occurred before ECS              | 5% (n = 4 of 77) |
| Mean days before ECS                 | 4 d |
| Range                                | 3-6 d |
| **CLL outcomes**                     |       |
| Resolution                           | 93% (n = 114 of 123) |
| Mean response time                   | 17 d |
| Range                                | 3-84 d |
| Did not receive treatment            | 63% (n = 60 of 95) |
| Treated                              | 37% (n = 35 of 95) |
| Unresolved                           | 4% (n = 5 of 123) |
| Mean follow-up time                  | 186 d |
| Range                                | 79-452 d |

CLL, chilblain-like lesions; ECS, extracutaneous symptoms; n, number of patients; N, number of patients in which clinical characteristic or outcome reported.
Data are presented as % (n of N) unless otherwise indicated.
* Some patients had CLL reports on both hands and feet, for a total >100%.

Characteristics of CLL

Location of CLL was reported in 2,429 cases. CLL were located on the feet in 90% (n = 2,195 of 2,429) of cases and on the hands in 18% (n = 431 of 2,429). Most CLL were described as erythematous to violaceous papules, macules, and/or plaques (Supplementary Table 1). Uncommon morphological features included erosions, vesicles, and bullae (Supplementary Table 2). In subgroup analysis of confirmed SARS-CoV-2 positive cases, 75% (n = 72 of 96) involved the feet only, whereas 11% (n = 11 of 96) involved the hands only, and 11% involved the hands and feet (n = 11 of 96) (Table 2).

Treatment

Treatment status was reported in 943 cases. Overall, 39% (n = 367 of 943) of CLL cases received treatment. The most commonly reported treatments were topical steroids (270), oral analgesics (123), warming (96), topical antimicrobials (38), systemic steroids (29), oral antihistamines (23), oral chloroquine/hydroxychloroquine (13), and oral nifedipine (13).

Resolution

Resolution outcomes were reported in a minority of cases (25%, n = 1,224 of 4,982) (Table 1). CLL resolved in 80% (n = 979 of 1,224) of cases in a mean of 16 days (range, 1-252 days). Among cases with resolved CLL, treatment data were available in 432 cases; 53% (n = 228 of 432) received some form of therapy. In resolved cases that received therapy, available data showed that topical steroids were used in 45% (n = 57 of 126) of cases, topical antimicrobials in 24% (n = 30 of 126), oral antihistamines in 19% (n = 24 of 126), oral analgesia in 55% (n = 69 of 126), systemic steroids in
8% (n = 10 of 126), and systemic antimicrobials in 6% (n = 7 of 126). The type of treatment was not reported in the other 102 cases that resolved with treatment. CLL were unresolved in 7% of cases (n = 91 of 1,224). Follow-up ranged from 9 to 495 days with a mean of 64 days. CLL recurrent in 13% (n = 154 of 1,224) of cases. Mean time to recurrence was 71 days (range, 5-196 days).

Of confirmed SARS-CoV-2 positive cases, CLL resolved in 93% of cases (n = 114 of 123) with a mean of 17 days (range, 3-84 days) (Table 2). According to available data, CLL resolved without treatment in 63% (n = 60 of 95). CLL were unresolved in 4% of cases (n = 5 of 123), with a mean follow-up of 186 days (range, 79-452 days).

Discussion

This review comprehensively summarizes available studies on CLL coinciding with the COVID-19 pandemic (n = 128 studies, 4,982 cases). Results of this review yield several important findings.

Demographics

There is lack of geographic diversity in available data, with 75% (n = 96 of 128) of studies from Europe and 16% (n = 21 of 128) from North America. More specifically, half of the studies were from Italy or Spain. This geographic bias is not well explained in the literature, although it may reflect an increased burden of disease, stricter confinement regulations, and/or a high volume of COVID-19 research publications originating in Italy. Additionally, this discrepancy may arise from heterogeneity in reporting dermatologic findings worldwide, particularly in areas with warmer climates such as Asia where pernio is rarely seen.

Consistent with prior literature, our review found that CLL occurred in a roughly equal sex ratio, and predominantly affected adolescents, although mean age of cases in our review was 25 years, slightly older than in previous reviews (21 years). Additionally, in line with previous reviews, the vast majority of CLL involved the feet, with the hands as the second most common site.

Extracutaneous symptoms

The majority of patients with CLL in this review were asymptomatic (63%), which is higher than previously reported (47% and 32.6%). This finding may be explained by more asymptomatic individuals seeking assessment due to increased media attention to “COVID toes.”

SARS-CoV-2 positive test rate

Overall, the SARS-CoV-2 positivity rate was 19% (n = 347 of 1,838), slightly higher than the positivity rate seen in prior reviews (15%). Our review included smaller case series and case reports, which made up a sizeable proportion of positive testing results; this may explain the difference observed. Our findings provide support for a potential causative role of SARS-CoV-2 in the development of CLL, posited to be via interferon-driven T-cell response to the virus.

Despite our results demonstrating a higher positivity rate than seen in prior work, positivity rates may still be underestimated for several reasons. The low proportion of positive IgG and IgM testing results may be because the viral load was insufficient to induce antibody formation and/or the patient developed an early and robust interferon type I response, muting early viral replication and not permitting the development of detectable IgM and IgG. Low rates of positive PCR tests may be due to rapid clearance of virus by the innate immune system, and tests occurring outside the time window of viral replication and shedding in the nasopharynx. Generalizability of IgA results is limited due to small sample size. With IgA being the most abundant antibody at mucosal sites, strong local protection may prevent viral spread and damage to the respiratory tract, explaining lack of symptoms and “immune memory” with few patients presenting with “memory” IgG; however, IgA testing results must be interpreted with caution since the high sensitivity can result in false positives.

Another potential explanation is that CLL are provoked by behavioral changes brought on by lockdowns and quarantines—specifically, altered peripheral circulation secondary to sedentary behaviors and inappropriate coverage of hands and feet when exposed to cold interior environments. As CLL are histopathologically and clinically identical to idiopathic chilblains, some of the CLL reported in the literature could be idiopathic and not related to SARS-CoV-2 infection; however, epidemiologic data comparing cohorts of chilblains before and during the pandemic do find some clear differences, not only in the frequency of reported chilblains, but also in the age and sex distribution.

Resolution

Our review supports a benign course for CLL, with 80% of CLL resolving in a mean of 16 days, and almost half receiving no treatment. Seven percent of CLL cases were unresolved, and 13% were recurrent. This is a higher relapse rate and lower resolution rate than seen in a previous review. This disparity is partially explained by longer-term follow-up available in recent studies, where large cohorts of patients were followed over months and multiple waves of the pandemic. It is thought that the lack of anti-SARS-CoV-2 antibodies makes these patients liable to reinfection and to new interferon response.

We have highlighted a number of topics for continued research. Although Fitzpatrick skin type was not reported in this review due to limited data, there is under-representation of patients with darker skin in the current literature around CLL. We suggest future studies regarding the...
diagnostic value of CLL given previous findings that acral lesions have a higher predictive value for positive COVID-19 tests than fever and are associated with high risk for household exposure to COVID-19. The prognostic value of CLL also warrants consideration as CLL have been repeatedly associated with good prognosis for COVID-19. Another topic of interest, beyond the scope of this review, is the relationship between COVID-19 vaccination and CLL.

There are several limitations to this review. First, without images, detailed descriptions of morphology, or laboratory workup to exclude other causes of CLL, we are unable to verify that all the cases included in this review truly represent CLL, potentially impacting the quality of results. Second, summaries were limited by heterogeneity in study data. For example, the number of cases with CLL both on the hands and feet were difficult to analyze due to heterogeneity in study data. Additionally, data on SARS-CoV-2 testing were available in only 37% of cases, often due to limited testing of asymptomatic cases, limiting the generalizability of our results. Finally, in large national or registry-based studies, the same case may have been reported several times, leading to an overestimate in number of cases. Where possible, efforts were made to avoid double-counting cases. Conclusions

This review summarizes 128 contributions representing almost 5,000 cases of CLL occurring during the COVID-19 pandemic. Results revealed that CLL affect mostly adolescents and young adults with a roughly equal sex ratio. Almost two-thirds of the patients had no ECS. In total, 19% of the patients were confirmed positive for SARS-CoV-2. CLL resolved in 80% of cases, in a mean of 16 days, with 53% of these patients receiving treatment. The causal relationship between CLL and SARS-CoV-2 is yet to be fully explained, but the relationship may be elucidated with widespread use of molecular and serologic SARS-CoV-2 testing and ongoing reporting of skin findings.

Conflict of interest

The authors declare no conflict of interest.

Supplementary materials

Supplementary material associated with this contribution may be found in the online version at doi:10.1016/j.clindermatol.2022.09.010.

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