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## Journal Pre-proof

Chilblain-like Lesions (CLL) Coinciding with the SARS-CoV-2 Pandemic

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**COVID-19: Important Updates and Developments****Edited by Franco Rongioletti, MD and Leonard J. Hoenig, MD****Title:** Chilblain-like Lesions (CLL) Coinciding with the SARS-CoV-2 Pandemic**Authors:** Samantha Y. Starkey, B.Sc.<sup>1</sup>; Kristie Mar, B.Sc.<sup>1</sup>; Nadia Kashetsky, M.Sc.<sup>2</sup>; Joseph M. Lam, MD, FRCPC<sup>3,4</sup>; Jan Dutz, MD, PhD, FRCPC<sup>3</sup>; Ilya Mukovozov, MD, MSc, PhD<sup>3</sup><sup>1</sup> Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada<sup>2</sup> Faculty of Medicine, Memorial University of Newfoundland, St. John's, Newfoundland and Labrador, Canada<sup>3</sup> Department of Dermatology and Skin Science, University of British Columbia, Vancouver, British Columbia, Canada<sup>4</sup> BC Children's Hospital, Vancouver, BC, Canada**Corresponding Author:** Ilya Mukovozov, MD, MSc, PhD<sup>3</sup>  
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Fax: 604 873-9919**Declarations of Interest:** None**Funding sources:** None**Acknowledgements:** None**Abstract word count:** 199**Manuscript word count:** 2200 [excluding abstract, references and tables]**Tables:** 2**Supplementary Tables:** 2**Supplementary Figures:** 1**Key Words:** COVID-19, chilblains, pernio, COVID toes

**ABSTRACT**

Chilblain-like lesions (CLL) coinciding with severe acute respiratory syndrome coronavirus 2 (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 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 and 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=2471/4472). Mean age was 25 years, ranging from 0 to 95 years. Most cases were not associated with extracutaneous symptoms (63%, n=1649/2636). Overall, 19% (n=347/1838) of patients tested positive for SARS-CoV-2 using polymerase chain reaction (PCR), serology, or tissue biopsy. Clinical course was generally benign with 80% (n=979/1224) of cases resolving, and 47% (n=204/432) resolving without receiving treatment. In summary, this review provides a comprehensive summary of CLL associated with SARS-CoV-2. CLL occurred at a mean age of 25 years with slight female predominance. The majority had negative COVID-19 testing, no extracutaneous symptoms, and resolved without recurrence.

## Introduction

Coronavirus 19 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and often presents with systemic, respiratory, gastrointestinal and/or ear nose and throat symptoms.<sup>1,2</sup> CLL, colloquially called “COVID toes,” are the most common cutaneous manifestation associated with COVID-19 (51.5%).<sup>3</sup> CLL morphologically resemble chilblains: acral erythematous to violaceous papules and plaques occasionally associated with pain and/or pruritus.<sup>4</sup>

Several reviews have summarized reports of CLL associated with SARS-CoV-2. CLL most often occur in younger individuals, mean age range seventeen to twenty-one, and in an approximately equal sex ratio.<sup>4-6</sup> CLL are almost always located on the feet and more rarely on the hands.<sup>4,5</sup> Prior systematic reviews reported that 36% to 47% of cases were not associated with extracutaneous symptoms (ECS), particularly in patients under twenty years old.<sup>4,5</sup> When ECS were present, they preceded CLL in 75% of cases, with an average latency period of sixteen days.<sup>5</sup> SARS-CoV-2 testing results reported an overall positivity rate of approximately 15%.<sup>4,5</sup>

This paper 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:

- **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 which 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](http://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 geographical restrictions. Level of evidence for included articles was determined using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence.<sup>7</sup>

Data extraction was performed by two reviewers using a standardized extraction form which 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 papers,<sup>8-13</sup> researchers published a follow-up on cases reported in prior work. Thirty-five studies (27%) were based in Italy, thirty in Spain (23%), twenty-one in France (16%), and nineteen in the United States (15%). According to available data, the majority of studies, 92% (n=110/119) reported cases from the first wave of the pandemic (spring and summer 2020),<sup>14,15</sup> while 3% (n=4/119) reported cases from the second wave (fall and winter 2020-2021) and 1% (n=1/119) from the third wave (mid-February 2021 to June 2021). The majority of studies were level of evidence 4 (66%, n=85/128) and 5 (25%, n=32/128) with the remaining studies level of evidence 3 (5%, n=7/128) and 2 (3%, n=4/128) (**Supplementary Table 1**).

### *Patient characteristics*

Available data showed that 55% (n=2471/4472) of cases were women. Mean age was 25 years, ranging from 0 to 95 years.

### *COVID Testing Results*

Overall, 19% (n=347/1838) 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 spike protein (**Table 1**). PCR test positivity rate was

9% (n=132/1503). Serological antibody testing (IgG and IgM) positivity rate was 10% (n=95/925). IgA, PCR of skin biopsy, and IgG against COVID spike protein positivity rates were 15% (n=30/204), 1% (n=1/75), and 29% (n=19/65) respectively.

### *Extracutaneous Symptoms*

According to available data, 63% (n=1649/2636) of cases were asymptomatic, while 37% (n=987/2636) had ECS (**Table 1**). Available data showed that 81% (n=544/670) of ECS occurred prior to the onset of CLL (mean: 13 days prior; range 1 to 270 days); 13% (n=84/670) concomitantly with CLL; and 6% (n=42/670) after the onset of CLL (mean: 7 days after, range 1 to 19 days).

A subgroup analysis of SARS-CoV-2 positive patients revealed that ECS were reported in 72% (n=90/125) of cases (**Table 2**). ECS occurred before CLL in 71% (n=55/77) of cases (mean: 55 days prior; range: 2 to 270 days); concomitantly in 23% (n=18/77) and after in 5% (n=4/77) (**Table 2**).

### *Characteristics of CLL*

Location of CLL was reported in 2429 cases. CLL were located on the feet in 90% (n=2195/2429) of cases and on the hands in 18% (n=431/2429). 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=72/96)



involved the feet only, while 11% (n=11/96) involved the hands only, and 11% involved the hands and feet (n=11/96) (**Table 2**).

### *Treatment*

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

### *Resolution*

Resolution outcomes were reported in a minority of cases (25%, n=1224/4982) (**Table 1**). CLL resolved in 80% (n=979/1224) of cases in a mean of 16 days (range 1 to 252 days). Among cases with resolved CLL, treatment data was available in 432 cases; 53% (n=228/432) received some form of therapy. In resolved cases that received therapy, available data showed that topical steroids were used in 45% (n=57/126) of cases, topical antibiotics in 24% (n=30/126), oral antihistamines in 19% (n=24/126), oral analgesia in 55% (n=69/126), systemic steroids in 8% (n=10/126), and systemic antibiotics in 6% (n=7/126). Type of treatment was not reported in the other 102 cases that resolved with treatment. CLL were unresolved in 7% of cases (n=91/1224). Follow up ranged from 9 to 495 days with mean 64 days. CLL recurred in 13% (n=154/1224) of cases. Mean time to recurrence was 71 days, range 5 to 196 days.

Of confirmed SARS-CoV-2 positive cases, CLL resolved in 93% of cases (n=114/123) with a mean of 17 days, range 3 to 84 days (**Table 2**). According to available data, CLL resolved

without treatment in 63% (n=60/95). CLL were unresolved in 4% of cases (n=5/123), with mean follow up 186 days, range 79 to 452 days.

## Discussion

This review comprehensively summarizes available studies on CLL coinciding with the COVID-19 pandemic (n= 128 studies, 4982 cases). Results of this review yield several important findings.

### *Demographics*

There is lack of geographic diversity in available data with 75% (n=96/128) of studies from Europe and 16% (n=21/128) from North America. More specifically, half of studies were from Italy or Spain. This geographic bias is not well explained in the literature, though it may reflect an increased burden of disease,<sup>16</sup> stricter confinement regulations,<sup>17</sup> and/or a high volume of COVID-19 research publications originating in Italy.<sup>18</sup> Additionally, this discrepancy may arise from heterogeneity in reporting dermatologic findings worldwide, particularly in areas with warmer climates like Asia where perniosis is rarely seen.<sup>19,20</sup> Fitzpatrick skin type may also play a role as the erythema typically associated with CLL may be more subtle in patients with darker skin.<sup>21</sup>

Consistent with prior literature, our review found that CLL occurred in a roughly equal sex ratio<sup>4,5</sup> and predominantly affected adolescents,<sup>4</sup> though mean age of cases in our review was 25 years, slightly older than in previous reviews (21 years)<sup>5,6</sup>. Additionally, in line with previous

reviews,<sup>4,5</sup> the vast majority of CLL involved the feet, with the hands as the second most common site.

### *Extracutaneous Symptoms*

The majority of cases of CLL in this review were asymptomatic (63%), which is higher than previously reported (47%<sup>5</sup> and 32.6%<sup>4</sup>). 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=347/1838), slightly higher than the positivity rate seen in prior reviews (15%).<sup>5,6</sup> Our review included smaller case series and case reports which make up a sizeable proportion of positive testing results, which 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.<sup>22</sup>

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.<sup>23</sup> Low rates of positive PCR tests may be due to rapid clearance of virus by the innate immune system<sup>24</sup> and tests occurring outside the time window of viral replication and shedding in the

nasopharynx.<sup>25-27</sup> Generalizability of IgA results is limited due to small sample size (n=204).

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<sup>28</sup>; however, IgA testing results must be interpreted with caution since the high sensitivity can result in false positives.<sup>6</sup>

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 cold interior environments.<sup>6,29-31</sup> 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,<sup>4,32,33</sup> 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 the age and sex distribution.<sup>30</sup>

### *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. 7% CLL cases were unresolved and 13% were recurrent. This is a higher relapse rate and lower resolution rate than seen in a previous review.<sup>5</sup> 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.<sup>9-11,34</sup> It is thought that the lack of anti-SARS-CoV-2 antibodies makes these patients liable to reinfection and to new interferon response.<sup>11</sup>

This review highlights a number of topics for continued research. Although Fitzpatrick skin type was not reported on in this review due to limited data, there is under-representation of patients with darker skin in the current literature around CLL.<sup>30,35-37</sup> Further, authors 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<sup>38</sup> and are associated with high risk for household exposure to COVID-19.<sup>39</sup> The prognostic value of CLL also warrants consideration as CLL have been repeatedly associated with good prognosis for COVID-19.<sup>40-43</sup> 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, 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 was only available in 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.

In conclusion, this review summarizes 128 papers representing almost 5,000 cases of CLL occurring during the COVID-19 pandemic. Results found that CLL affect mostly adolescents and young adults with a roughly equal sex ratio. Almost two-thirds of cases had no ECS. In total, 19% of cases were confirmed positive for SARS-CoV-2. CLL resolved in 80% of cases, in a

mean of 16 days, with 53% of these cases 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 serological SARS-CoV-2 testing and ongoing reporting of skin findings.

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**Table 1:** Clinical characteristics, COVID-19 testing results and outcomes of chilblain-like lesions (CLL) coinciding with the COVID-19 pandemic.

Clinical Characteristics and Outcomes		Cases, % (n/N)
<b>Patient Characteristics (n=4982)</b>		
Sex	Men	45% (n = 2001/4472)
	Women	55% (n = 2471/4472)
Age, years	Mean	25 (n = 2326/4982)
	Range	0 to 95 years
<b>CLL Information</b>		
Location <sup>a</sup>	Feet	90% (n = 2195/2429)
	Hands	18% (n = 431/2429)
	Other	1% (n = 20/2429)
<b>Extracutaneous Symptoms (ECS)</b>		
Presence of ECS	Yes	37% (n = 987/2636)
	No (asymptomatic)	63% (n = 1649/2636)
<b>Timing of CLL</b>		
After ECS	Mean, days (range)	81% (n = 544/670) 13 (1 to 270)
	Concomitant with ECS	13% (n = 84/670)
Before ECS	Mean, days (range)	6% (n = 42/670) 7 (1 to 19)
<b>SARS-CoV-2 Infection Information</b>		
	Positive SARS-CoV-2 Test	19% (347/1838)
	Negative SARS-CoV-2 Test	81% (1491/1838)
	Positivity by Type of Test	
	PCR	9% (n = 132/1503)
	Serological test (IgG, IgM)	10% (n = 95/925)
	IgA	15% (n = 30/204)
	PCR on biopsy	1% (n = 1/75)
	IgG against spike protein	29% (n = 19/65)
<b>CLL Outcomes</b>		
	Resolved	80% (n = 979/1224)
	Mean response time	16 days
	Range	1 to 252 days
	No treatment	47% (n = 204/432)

Treated	53% (n = 228/432)
Systemic corticosteroids	8% (n = 10/126)
Topical corticosteroids	45% (n = 57/126)
Oral analgesia	55% (n = 69/126)
Oral antihistamines	19% (n = 24/126)
Systemic antimicrobials	6% (n = 7/126)
Topical antimicrobials	24% (n = 30/126)
Chloroquine, hydroxychloroquine	5% (n = 6/126)
Unresolved	7% (n = 91/1224)
Mean follow up time	64 days
Range	9 to 495 days
Recurrent	13% (n = 154/1224)
Mean time to recurrence	71 days
Range	5 to 196 days

**CLL:** chilblain-like lesions; **ECS:** extracutaneous symptoms; **PCR:** polymerase chain reaction

<sup>a</sup> Some patients had CLL reports on both hands and feet, for a total >100%

n: number of patients

N: number of patients in which clinical characteristic or outcome reported



**Table 2:** Clinical characteristics and outcomes of chilblain-like lesions (CLL) coinciding with the COVID-19 pandemic in cases with positive COVID-19 testing.

Clinical Characteristics and Outcomes		Cases, % (n/N)
<b>Patient Characteristics (n=188)</b>		
<b>Sex</b>	Men	50% (n = 56/111)
	Women	50% (n = 55/111)
<b>Age, years</b>	Mean	30 (n = 114/188)
	Range	7 to 80 years
<b>CLL Information</b>		
<b>Location<sup>a</sup></b>	Feet	86% (n = 83/96)
	Hands	23% (n = 22/96)
	Other	4% (n = 4/96)
<b>Extracutaneous Symptoms (ECS)</b>		
<b>Presence of ECS</b>	Yes	72% (n = 90/125)
	No (asymptomatic)	28% (n = 35/125)
<b>Timing of CLL</b>		
	CLL occurred after ECS	71% (n = 55/77)
	Mean days after ECS	55 days
	Range	2 to 270 days
	Concomitant with ECS	23% (n = 18/77)
	CLL occurred before ECS	5% (n = 4/77)
	Mean days before ECS	4 days
	Range	3 to 6 days
<b>CLL Outcomes</b>		
	Resolution	93% (n = 114/123)
	Mean response time	17 days
	Range	3 to 84 days
	Did not receive treatment	63% (n = 60/95)
	Treated	37% (n = 35/95)
	Unresolved	4 % (n = 5/123)
	Mean follow up time	186 days
	Range	79 to 452 days

**CLL:** chilblain-like lesions; **ECS:** extracutaneous symptoms

<sup>a</sup> Some patients had CLL reports on both hands and feet, for a total >100%

n: number of patients

N: number of patients in which clinical characteristic or outcome reported

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