

SHORT PAPER

Do we have serological evidences that chilblain-like lesions are related to SARS-CoV-2? A review of the literature

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Abstract

The outbreak of chilblain-like lesions (CLL) coincidentally to the COVID-19 pandemic is a topic of great concern. SARS-CoV-2 was initially hypothesized as the etiologic agent of CLL, but, since nasopharyngeal swabs seldom resulted positive, dermatologists' attention focused on the search for specific SARS-CoV-2 antibodies. Many papers were published contemporarily on this topic, reporting limited case series. We reviewed the English literature up to the first July 2020 and, excluding single case reports, we considered 13 studies that serologically investigated 220 patients. The presence of specific antibodies was detected in 18 subjects (8.2%): isolated IgA were found in 6 patients, IgA and IgG in 1, isolated IgG in 5, and IgM in 2. In 4 patients, isotypes were not specified. Our review demonstrated a high prevalence of negative serological results in CLL: antibodies were observed only in a few patients, that are even less excluding those with positive IgA, not clearly involved in the pathogenesis of the disease. In conclusion, although it is still uncertain whether CLL are related to SARS-CoV-2 infection, patients affected by CLL seem not to be prone to shedding the virus, hence, if they are asymptomatic, we can reassure them, thus avoiding hospital referral.

KEYWORDS

acro-ischemia, chilblain-like lesions, COVID-19, IgG, IgM, pernio-like lesions, SARS-CoV-2, serological test

1 | INTRODUCTION

The outbreak of chilblain-like lesions (CLL) coincidentally to the COVID-19 pandemic is a topic of great concern.¹ SARS-CoV-2 was hypothesized as the etiologic agent of CLL, initially on the basis of the temporal correlation between the “burst” of skin manifestations and the viral pandemic. However, it has been shown that CLL are not related to an acute infection, since real-time reverse transcription polymerase chain reaction (rt-PCR) tests from nasopharyngeal swabs seldom resulted positive.¹⁻⁹

Therefore, dermatologists' attention shifted to the search for specific SARS-CoV-2 antibodies. Many papers were published

contemporarily on this topic, reporting limited case series. The aim of our review is to collect more data concerning seroprevalence and to better understand the role of SARS-CoV-2 in the development of CLL.

2 | MATERIALS AND METHODS

2.1 | Data source and search strategy

We reviewed the English literature up to the first July 2020 in the PubMed MEDLINE database using combinations of the key search terms “acral,” “acro-ischemic,” “acro-syndrome,” “chilblain,” “chilblain-like,” “COVID-19,” “pernio,” “pernio-like,” “perniosis,”

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"pseudochilblain," and "SARS-CoV-2." Search terms were used in combinations.

2.2 | Study selection

The search was limited to articles published in English. We included only case series, clearly declaring that a search for SARS-CoV-2 specific antibodies had been performed. Single case reports were excluded.

2.3 | Data extraction and quality assessment

Data were independently extracted by two authors (MM and RB), then the results of data extraction were compared.

3 | RESULTS

The initial research on PubMed returned 72 papers focusing on CLL and SARS-CoV-2.

We retrieved 13 articles reporting serological studies performed on case series that included at least 8 patients (Table 1).

Twelve studies took place in Europe and the last one is an observational survey conducted in 8 US states. A total of 220 patients were serologically investigated.

Testing methods were various: chemiluminescent immunoassays were used in 3 studies, chromatographic immunoassay was used by 2 groups, enzyme linked immunosorbent assays (ELISA) in other 2, one study used both a chemiluminescent immunoassay and an ELISA, and one both chromatographic and ELISA. In 4 papers test types were not specified.

Performances declared in the manufacturers' package insert of each test are reported in Table 2.

The presence of specific antibodies was detected in 18/220 (8.2%) cases. The detected isotypes were: isolated IgA 6 (2.7%); IgA and IgG 1 (0.4%), isolated IgG 5 (2.3%); IgM 2 (0.9%). In 4 cases, the isotype was not specified.

The timing between symptom onset and test execution is reported in 4 studies, with an overall mean period of 21.49 ± 18.89 days (Rizzoli et al: 51.25 ± 25.85 ; Herman et al: 13.16 ± 7.74 ; Roca-Ginés et al: 13.25 ± 8.11 ; Rouanet et al: 25.44 ± 7.68).^{1,7,11,14} One study declared only the total median (25 days).⁶ One hundred and ninety-two patients also underwent rt-PCR, resulted negative in all cases.

4 | DISCUSSION

At the beginning of the CLL epidemic, a role of SARS-CoV-2 was hypothesized only on the basis of the temporal correlation with the COVID-19 pandemic, searching for evidence from nasopharyngeal

swabs. It is now clear that CLL do not represent an acute cutaneous manifestation of SARS-CoV-2, hence swabs are completely useless to confirm the infection. The attention of the scientific community therefore shifted to serology, assuming that specific antibodies may validate this hypothesis.

The present review shows a high prevalence of negative serological results in CLL, indicating that this is a wrong strategy to demonstrate the role of coronavirus in CLL. In fact, antibodies were observed only in a limited percentage of patients, which becomes very low (5.45%) if we exclude patients with IgA, whose role remains doubtful in the pathogenesis of the disease.

Some considerations and hypotheses can be raised to explain this finding.

1. We are observing true chilblains: Three groups support this theory, considering these skin lesions caused by lifestyle changes due to containment and lockdown measures.^{7,10,11} However, although this may be true for some of these cases, given the large number of new reports of CLL coincidentally with the COVID-19 pandemic, it is not sufficient to explain all the cases. Moreover, mean European temperatures during the first months of 2020 were similar or higher compared to those of the last 29 years, and solely the sedentary habits and barefoot walking at home seem inadequate to justify an epidemic of CLL.
2. Serological tests are not reliable: This was particularly true with the initially-available tests, since they had been rapidly developed and placed on the market with limited validation. However, we can exclude this hypothesis because serological tests showed excellent clinical performance in real life¹ and the authors used eight different types of test, achieving similar findings.
3. Patients with mild disease tend not to have an adequate antibody response: Higher levels of IgM and IgG have been found in the second and third week of illness, then IgM begins to decline and almost disappears by week 7, while IgG persists.^{12,13} The duration of their persistence still remains unknown: data suggest a serological profile similar to SARS-CoV,¹² although asymptomatic/ paucisymptomatic patients seem to present lower levels of specific antibodies compared to severe disease. Lower levels do not mean an absence of antibodies, hence we can also exclude this hypothesis. Another issue could be the timing in which tests had been performed, since a sufficient time lapse is necessary to develop antibodies. This information is reported only in four studies, and the timing proved adequate to detect antibodies in most cases.
4. Cytotoxic CD8 T cells hypothesis: Locally recruited cytotoxic CD8 T cells could be the effector of skin lesions. During mild forms of the disease, such as those developing CLL, T cell exhaustion, and viral-associated immunosuppression may reduce the production of SARS-CoV-2 specific antibodies, therefore an incomplete viral clearing may induce delayed cutaneous lesions without detectable antibodies.⁹
5. Interferon hypothesis: In genetically predisposed individuals the contact with SARS-CoV-2 triggers a robust interferon response, of

TABLE 1 Review of the literature

First author	No.	SSR (positive /total)	Serological test (ST)				Comment of the authors	
			Type of ST	Antibodies (positive /total)	IgM (positive /total)	IgG (positive /total)		IgA (positive /total)
Caselli	38	0/38	RCIELISA	0/38	0/38/	0/380/38	0/38	<ul style="list-style-type: none"> Clustering of skin lesions during peak pandemic suggests some nonrandom association No data to support the relationship of the outbreak of pseudo-chilblain with SARS-CoV-2 infection
Colonna	8	0/8	ACI	1/8	/	1/8	/	<ul style="list-style-type: none"> Uncertain relationship between chilblain-like lesions and SARS-CoV-2
El Hachem	19	0/19	CMI/ELISA	7/19	//	0/191/19 ^a	6/19 ^a	<ul style="list-style-type: none"> Unlikely idiopathic pemphigus IgA strongly suggests a relationship between chilblain-like lesions and SARS-CoV-2
Freeman	20	NA	NA	6/20	2/6: IgM+/IgG-, 4/6: not specified			<ul style="list-style-type: none"> Pernio-like skin changes may suggest SARS-CoV-2 infection and should prompt confirmatory testing.
García-Lara	9	0/2	NA	0/9	0/9	0/9	0/9	<ul style="list-style-type: none"> It is difficult to establish a relationship with SARS-CoV-2 infection
Herman	31	0/31	CLIA	0/31	0/31	0/31	/	<ul style="list-style-type: none"> Chilblains appeared not to be directly associated with SARS-CoV-2 Skin lesions may be caused by lifestyle changes brought on by containment and lockdown measures.
Kanitakis	17	0/17	NA	0/17	Not specified			<ul style="list-style-type: none"> Pathological findings support the absence of a direct relationship between chilblain and SARS-CoV-2
Mahieu	10	0/10	ELISA	0/10	/	0/10	0/10	<ul style="list-style-type: none"> Inability of the host immune system during mild form of the disease to completely clear the virus may explain these delayed cutaneous lesions without detectable antibody production
Martinez	19	0/19	NA	3/19	/	3/19	1/19	<ul style="list-style-type: none"> A relationship with SARS-CoV-2 could not be demonstrated in most cases
Neri	8	0/8	CLIA2	0/8	0/8	0/8	/	<ul style="list-style-type: none"> Observed chilblains are primary and affect predisposed subjects due to cold exposure in the lockdown period
Rizzoli	12	0/12	RCI2	1/12	0/12	1/12	/	<ul style="list-style-type: none"> CLL are not a specific marker of SARS-CoV-2 Testing a larger amount of patients with CLL Investigate etiologic agents other than SARS-CoV-2
Roca-Ginés	20	0/20	ELISA	0/20	0/20	0/20	0/20	<ul style="list-style-type: none"> The clinical, histologic, and laboratory test results were compatible with a diagnosis of pemphigus, and no evidence was found to support the implication of SARS-CoV-2 infection
Rouanet	9	0/7	CMI/IA	0/9	/	0/9	/	<ul style="list-style-type: none"> Results do not support a direct effect of SARS-CoV-2

Abbreviations: ACI, automated chromatographic immunoassay (LIAISON SARS-CoV-2 S1/S2 IgG test kit); CLIA, fully automated quantitative chemiluminescent immunoassays (Maglumi 2019-nCoV IgG and IgM); CLIA2, chemiluminescent immunoassays (Flash-SARS-CoV-2 IgG and IgM); CMI/IA, chemiluminescent microparticle immunoassay (Abbott Laboratories, The United States); ELISA, enzyme linked immunosorbent assay (Euroimmun, Germany); NA, not available/not specified; RCI, rapid chromatographic immunoassay (VivaDiag COVID-19 IgM/IgG Rapid Test); RCI2, rapid chromatographic immunoassay (SD Biosensor COVID-19 IgM/IgG Duo assay); SSR, SARS-CoV-2 Swab Result (rt-PCR); ST, serological test.

^aborderline results in 3/19.

TABLE 2 Manufacturers' declared performances of serological test

Name of test	Sensitivity	Specificity
Abbott ARCHITECT SARS-CoV-2 IgG	100% (>14 days after the symptom onset)	99.6% (>14 days after the symptom onset)
Euroimmun ELISA Anti-SARS-CoV-2 IgA and IgG	90% (CI 74.4%; 96.5%)	100% (CI 95.4%; 100%)
iFlash-SARS-CoV-2 IgG and IgM	IgM: >90% IgG: >95%	IgM: >95% IgG: >95%
LIAISON SARS-CoV-2 S1/S2 IgG test kit	97.4% (CI 86.8%-99.5%)	98.5% (CI 97.5%-99.2%)
Maglumi 2019-nCoV IgG and IgM	IgM: 78.65% IgG: 91.21%	IgM: 97.50% IgG: 97.33%
SD Biosensor COVID-19 IgM/IgG Duo assay	99.10% (>14 days after the symptom onset)	95.09% (>14 days after the symptom onset)
VivaDiag COVID-19 IgM/IgG Rapid Test	IgM: 94.4% IgG: 100% (11-24 days after the symptom onset)	IgM: 100% IgG: 100%
COVID-19 ELISA Kit, Vircell, IgM/IgG + IgA	IgM + IgA: 98% IgG: 98%	IgM + IgA: 98% IgG: 98%

which chilblains are the cutaneous expression. This hypothesis is supported by the fact that chilblains are a prototypical sign of a few inherited disorders of innate immunity, characterized by a strong interferon signature and a severe microangiopathy (ie, interferonopathies). This strong IFN-I response would mute early viral replication, clearing the virus without intervention of the adaptive immune system, thus avoiding the development of detectable IgM/IgG.¹

6. SARS-CoV-2 is not the etiologic agent of CLL: Finally, we could consider the involvement of another viral agent in the epidemic of CLL, and the seldom test-positivity to SARS-CoV-2 may therefore be only a casual finding. However, a viral outbreak during another viral pandemic seems highly improbable.

In conclusion, while recent findings seem to suggest that SARS-CoV-2 could have a pathogenetic role in the development of CLL, also serological screening failed to prove that acral skin lesions are a specific marker of SARS-CoV-2 infection. Further studies are needed to obtain a definitive confirmation. In the meanwhile, it seems that patients affected by CLL are not prone to shedding the virus; consequently, in the case of otherwise asymptomatic patients, we can reassure them, without referring them to hospital to perform any sort of COVID-19 test, or quarantining them.

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CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in PubMed database at <https://pubmed.ncbi.nlm.nih.gov/>

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