# New insights in COVID-19-associated chilblains: A comparative study with chilblain lupus erythematosus

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# New insights in COVID-19-associated chilblains: a comparative study with chilblain lupus erythematosus

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Funding sources: None
Conflicts of Interest: None
IRB approval status: Approved by the institutional review board of HUPNVS, Paris 7 University, AP-HP (IRB 00006477)
Statement of any prior presentation: none

Manuscript word count: 499 words
References: 5
Figures: 0
Supplementary figures: 0
Tables: 2
Supplementary tables: 0

**Abbreviation and acronym list:**

Epidemic chilblain: EC

Chilblain lupus erythematosus: CLE

Type-1 interferon: IFN-1

Plasmacytoid dendritic cells: pDCs

Antineutrophils cytoplasmic antibodies: ANCA

*To the Editor*: An unexpected outbreak of chilblain has been reported in association with Coronavirus disease 19 (COVID-19)[1]. SARS-CoV-2 infection has been demonstrated in a few documented cases of chilblain. Chilblain may also be observed in acquired lupus and rarely as a manifestation of a familial disorder related to interferonopathies. To enhance understanding of this «epidemic chilblain» (EC) and their relevance to SARS-CoV-2 infection, we studied clinical, haemato-immunological, histopathological, immunohistochemical and virological characteristics of 7 EC cases and compared them with 11 previous cases of chilblain lupus erythematosus (CLE).

EC patients were included between February and April 2020 and were suspected of COVID-19 because they presented with COVID-19 symptoms or were in close contact with presumed/confirmed COVID-19 patients. Exclusion criteria were patients with previous chilblain episode, cold exposure preceding chilblain occurrence and history of known auto-immune disorder. For each patient, we collected demographic data, clinical and laboratory tests, including exhaustive haemato-immunological screening, cutaneous histology (including immunostaining for CD123, a plasmocytoid dendritic cells (pDCs) marker, and MxA, a type-I interferon (IFN-I)-induced protein) and virological studies.

The clinico-biological findings of EC and CLE cases are summarized in Table 1. Hands, ears, or nose localisation were more frequently observed in CLE group (82% vs 0%). Anti-nuclear antibodies were only detected in the CLE group (91% vs 0%). Age of onset of chilblain, sex, pre-existing Raynaud's phenomenon and other immunological abnormalities did not differ between groups. Antineutrophils cytoplasmic antibodies (ANCA) and lupus-type circulating anticoagulant were found in two and one EC patients, without any clinical manifestation of ANCA vasculitis or thrombosis. No EC patient had cryoprotein, cold agglutinin or anticardiolipin antibodies.

Our 7 EC cases were histologically similar to CLE. High expression of CD123 and MxA were observed in both groups (table 2).

SARS-CoV-2 RNA detection performed at a median delay of 23 days after symptoms onset (10-36) was negative in nasopharyngeal, skin biopsies and plasma samples. Repeated SARS-CoV-2 IgG/IgA

tests were negative for all patients except for one case who showed an isolated IgA positivity (time between first symptoms and serologies ranged 21-51 days).

Active Human herpes virus type 6, 7, 8 and Epstein Barr virus infections were excluded by reliable tests (PCR).

These results confirmed that chilblains may be considered as a manifestation of high production of IFN-I as observed in interferonopathies. These patients may exhibit only IFN-I associated symptoms or minor forms of COVID-19 infection. High level of IFN-I was associated with moderate cases of COVID-19[2]. Interferon-induced proteins such as IFITM (interferon-induced trans-membrane) 1, 2 and 3 inhibit early replication of several enveloped RNA viruses, such as MERS-coronaviruses[3]. In addition, active viral replication may not be necessary to mount an efficient IFN response in SARS-CoV infection[4]. IFN-I may also suppress antibody responses that might explains the negativity of the serologies in most patients with EC[5].

SARS-Cov-2 infection may induce in some predisposed patients a high production of IFN-I responsible for a high innate immune protective response. This hypothesis provides additional arguments to propose early IFN treatment for infected high-risk patients.

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149 **TABLES**

**Table 1. Clinical and biological findings in EC and CLE**

| **Variable** | **EC**<br>**n = 7** | **CLE**<br>**n = 11** | ***P***<br>**Value** |
|---|---|---|---|
| Female, n (%) | 4 (57) | 7 (64) | 1 |
| Mean age (SD) | 42 (10) | 49 (15) | 0.27 |
| Previous Raynaud's phenomenon, No (%) | 4 (57) | 4 (36) | 0.63 |
| Previous other cutaneous symptoms, No (%) | 3[a] (43) | 8 (73) | 0.33 |
| Feet-localized localisation, No (%) | 7 (100) | 2 (18) | <0.01 |
| COVID-19 symptoms, No (%) | 5 (71) | NA | - |
| Potential SARS-CoV-2 contact, No (%) | 4 (57) | NA | - |
| Positive anti-nuclear antibodies, No (%) | 0 (0) | 10 (91) | <0.01 |
| Presence of other immunological abnormalities, No (%) | 3[b] (43) | 9 (82) | 0.14 |

150 Abbreviations : SD= standard deviation ; NA= not applicable.
151 [a]Two patients had acrocyanosis and one patient had photosensitivity.
152 [b]Two patients had ANCA and one patient had lupus-type circulating anticoagulant.
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**Table 2. Histological and Immunohistochemical comparison between EC and CLE**

| Variable | | EC n = 7 | CLE n = 11 | *P* Value |
|---|---|---|---|---|
| **Epidermis** | | | | |
| Lymphocyte exocytosis, No (%) | | 3 (43) | 7 (64) | 0.63 |
| Confluent necrosis, No (%) | | 1 (14) | 0 (0) | 0.39 |
| Apoptotic keratinocytes, No (%) | | 2 (29) | 4 (36) | 1 |
| Vacuolized basement membrane zone, No (%) | | 1 (14) | 8 (73) | **0.049** |
| **Papillary dermis** | | | | |
| Oedema, No (%) | | 4 (57) | 2 (18) | 0.14 |
| Lymphocyte infiltrate intensity score[a], median (ranges) | | 2 (1 – 3) | 2 (1 - 3) | 0.34 |
| Lymphocyte infiltrate localization, No (%) | | | | |
| | Perivascular localisation | 7 (100) | 11 (100) | 1 |
| | Interstitial localisation | 3 (43) | 8 (73) | 0.33 |
| Other inflammatory cell infiltrate, No (%) | | 2 (29) | 3 (27) | 1 |
| Lymphocytic vasculitis, No (%) | | 5 (71) | 1 (9) | **0.01** |
| Congestive vessels, No (%) | | 2 (29) | 0 (0) | 0.13 |
| Red blood cell extravasation, No (%) | | 4 (57) | 1 (9) | **0.047** |
| **Reticular and deep dermis** | | | | |
| Lymphocyte infiltrate intensity score[a], median (range) | | 2 (1 - 3) | 2 (0 - 3) | 0.77 |
| Lymphocyte infiltrate localization, No (%) | | | | |
| | Perivascular | 7 (100) | 10 (91) | 1 |
| | Interstitial | 0 (0) | 0 (0) | 1 |
| | Peri-eccrine | 6 (86) | 7/10 (70)[b] | 0.60 |
| | Peri-neural | 4 (57) | 7/9 (78)[c] | 0.59 |
| Other inflammatory cell infiltrate, No (%) | | 2 (29) | 3 (27) | 1 |
| Lymphocytic vasculitis, No (%) | | 4 (57) | 7 (64) | 1 |
| Leucocytoclasic vasculitis, No (%) | | 1 (14) | 1 (9) | 1 |
| Congestive vessels, No (%) | | 3 (43) | 1 (9) | 0.24 |

| | | | |
|---|---|---|---|
| Median of neural section (range) | 5 (2 – 9) | 3 (0 – 4) | **0.008** |
| **Hypodermis**[d] | | | |
| Perivascular lymphocyte infiltrate, No (%) | 2/2 (100) | 0/2 (0) | 0.33 |
| **Immunohistochemical features** | | | |
| Case with MxA+ cells, No (%) | 7 (100) | 10/10 (100)[e] | 1 |
| MxA expression, median value (range) | 180 (105 – 280) | 270 (120 – 300) | 0.28 |
| Case with CD123+ cells, No (%) | 6 (86) | 9/10 (90)[e] | 1 |
| CD123 expression, median value (range) | 50 (0 – 60) | 15 (0 – 100) | 0.32 |
| **Positive cutaneous DIF, No (%)** | 0/3 (0)[f] | 1/2 (50)[g] | 0.4 |

Abbreviations: SD = standard deviation; MxA = myxovirus resistance protein A; DIF = Direct Immunofluorescence

[a] Intensity was scored as follow: 0= absence, 1= rare, 2= moderated, 3= intense;

[b] One of CLE biopsy did not show eccrine gland;

[c] Two of CLE did not show nerve;

[d] Hypodermis was observed in 2 biopsies in each groups;

[e] One LCE could not have immunohistochemistry analyse;

[f] 3 DIF were performed in the epidemic chilblain group;

[g] 2 DIF were performed in the lupus chilblain group; SD = standard deviation.

An unexpected outbreak of chilblain has been observed with Coronavirus disease 19 (COVID-19)[1,6]. SARS-CoV-2 infection has been demonstrated in a few documented cases of chilblain[7–9]. Chilblain may also be observed in acquired lupus and rarely as a manifestation of a familial disorder related to interferonopathies[10].

To enhance understanding of these « epidemic chilblains » (EC) and their relevance to SARS-CoV-2 infection, we studied clinical, haemato-immunological, histopathological, immunohistochemical and virological characteristics of seven EC cases and compared them with lupus chilblain erythematosus (CLE).

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