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

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46 **Abbreviation and acronym list:**

47 Epidemic chilblain: EC

48 Chilblain lupus erythematosus: CLE

49 Type-1 interferon: IFN-1

50 Plasmacytoid dendritic cells: pDCs

51 Antineutrophils cytoplasmic antibodies: ANCA

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69 *To the Editor:* An unexpected outbreak of chilblain has been reported in association with
70 Coronavirus disease 19 (COVID-19)¹. SARS-CoV-2 infection has been demonstrated in a few
71 documented cases of chilblain. Chilblain may also be observed in acquired lupus and rarely as a
72 manifestation of a familial disorder related to interferonopathies. To enhance understanding of this
73 «epidemic chilblain» (EC) and their relevance to SARS-CoV-2 infection, we studied clinical, haemato-
74 immunological, histopathological, immunohistochemical and virological characteristics of 7 EC cases
75 and compared them with 11 previous cases of chilblain lupus erythematosus (CLE).
76 EC patients were included between February and April 2020 and were suspected of COVID-19
77 because they presented with COVID-19 symptoms or were in close contact with
78 presumed/confirmed COVID-19 patients. Exclusion criteria were patients with previous chilblain
79 episode, cold exposure preceding chilblain occurrence and history of known auto-immune disorder.
80 For each patient, we collected demographic data, clinical and laboratory tests, including exhaustive
81 haemato-immunological screening, cutaneous histology (including immunostaining for CD123, a
82 plasmacytoid dendritic cells (pDCs) marker, and MxA, a type-I interferon (IFN-I)-induced protein) and
83 virological studies.
84 The clinico-biological findings of EC and CLE cases are summarized in Table 1. Hands, ears, or nose
85 localisation were more frequently observed in CLE group (82% vs 0%). Anti-nuclear antibodies were
86 only detected in the CLE group (91% vs 0%). Age of onset of chilblain, sex, pre-existing Raynaud's
87 phenomenon and other immunological abnormalities did not differ between groups. Antineutrophils
88 cytoplasmic antibodies (ANCA) and lupus-type circulating anticoagulant were found in two and one
89 EC patients, without any clinical manifestation of ANCA vasculitis or thrombosis. No EC patient had
90 cryoprotein, cold agglutinin or anticardiolipin antibodies.
91 Our 7 EC cases were histologically similar to CLE. High expression of CD123 and MxA were observed
92 in both groups (table 2).
93 SARS-CoV-2 RNA detection performed at a median delay of 23 days after symptoms onset (10-36)
94 was negative in nasopharyngeal, skin biopsies and plasma samples. Repeated SARS-CoV-2 IgG/IgA

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

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

99

100 These results confirmed that chilblains may be considered as a manifestation of high production of
101 IFN-I as observed in interferonopathies. These patients may exhibit only IFN-I associated symptoms
102 or minor forms of COVID-19 infection. High level of IFN-I was associated with moderate cases of
103 COVID-19². Interferon-induced proteins such as IFITM (interferon-induced trans-membrane) 1, 2 and
104 3 inhibit early replication of several enveloped RNA viruses, such as MERS-coronaviruses³. In addition,
105 active viral replication may not be necessary to mount an efficient IFN response in SARS-CoV
106 infection⁴. IFN-I may also suppress antibody responses that might explains the negativity of the
107 serologies in most patients with EC⁵.

108 SARS-Cov-2 infection may induce in some predisposed patients a high production of IFN-I responsible
109 for a high innate immune protective response. This hypothesis provides additional arguments to
110 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 n = 7	CLE n = 11	P 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 ^aTwo patients had acrocyanosis and one patient had photosensitivity.152 ^bTwo 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	
Leucocytoclastic 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

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

156 Immunofluorescence

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

158 ^b One of CLE biopsy did not show eccrine gland;

159 ^c Two of CLE did not show nerve;

160 ^d Hypodermis was observed in 2 biopsies in each groups;

161 ^e One LCE could not have immunohistochemistry analyse;

162 ^f 3 DIF were performed in the epidemic chilblain group;

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

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176 An unexpected outbreak of chilblain has been observed with Coronavirus disease 19 (COVID-19)^{1,6}.
177 SARS-CoV-2 infection has been demonstrated in a few documented cases of chilblain⁷⁻⁹.
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179 related to interferonopathies¹⁰.
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