Clinical, Laboratory, and Interferon-Alpha Response Characteristics of Patients With Chilblain-like Lesions During the COVID-19 Pandemic

Thomas Hubiche, MD; Nathalie Cardot-Leccia, MD; Florence Le Duff, MD; Barbara Seitz-Polski, MD, PhD; Pascal Giordana, MD; Christine Chiaverini, MD, PhD; Valérie Giordanengo, MD, PhD; Géraldine Gonfrier, MD; Vincent Raimondi, MD; Olivier Bausset, PharmD; Zoubir Adjitoutah, PharmD; Margaux Garnier, MD; Fanny Burel-Vandenbos, MD, PhD; Bérengère Dadone-Montaudié, MD, PhD; Véronique Fassbender, MD; Aurélia Palladini, MD; Johan Courjon, MD; Véronique Mondain, MD; Julie Contenti, MD, PhD; Jean Dellamonica, MD, PhD; Georges LeFatheriotis, MD, PhD; Thierry Passeron, MD, PhD

IMPORTANCE Chilblain-like lesions have been reported during the coronavirus 2019 (COVID-19) pandemic. The pathophysiology of such manifestations remains largely unknown.

OBJECTIVE To perform a systematic clinical, histologic, and biologic assessment in a cohort of patients with chilblain-like lesions occurring during the COVID-19 pandemic.

DESIGN, SETTING, AND PARTICIPANTS In this prospective case series carried out with a COVID-19 multidisciplinary consultation group at the University Hospital of Nice, France, 40 consecutive patients presenting with chilblain-like lesions were included.

MAIN OUTCOMES AND MEASURES Patients underwent a thorough general and dermatologic examination, including skin biopsies, vascular investigations, biologic analyses, interferon-alpha (IFN-α) stimulation and detection, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) and serologic analysis.

RESULTS Overall, 40 consecutive patients with chilblain-like lesions were included. Most patients were young, with a median (range) age of 22 (12-67) years; 19 were male and 21 were female. The clinical presentation was highly reproducible with chilblain-like lesions mostly on the toes. Bullous and necrotic evolution was observed in 11 patients. Acrocyanosis or cold toes were reported in 19 (47.5%) cases. Criteria compatible with COVID-19 cases were noted in 11 (27.5%) within 6 weeks prior to the eruption. The real-time PCR (rt-PCR) testing results were negative in all cases. Overall, SARS-CoV-2 serology results were positive in 12 patients (30%). D-dimer concentration levels were elevated in 24 (60.0%) cases. Cryoglobulinemia and parvovirus B19 serologic results were negative for all tested patients. The major histologic findings were features of lymphocytic inflammation and vascular damage with thickening of venule walls and pericyte hyperplasia. A significant increase of IFN-α production after in vitro stimulation was observed in the chilblain population compared with patients with mild-severe acute COVID-19.

CONCLUSIONS AND RELEVANCE Taken together, our results suggest that chilblain-like lesions observed during the COVID-19 pandemic represent manifestations of a viral-induced type I interferonopathy.

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range of cutaneous manifestations, including chilblain-like lesions, have been described in association with severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection during the coronavirus 2019 (COVID-19) pandemic.1 Chilblain-like lesions have been occurring more frequently than expected, and studies have begun to explore the potential link with SARS-CoV-2 infection vs other plausible etiologies.2-4 The aim of this case series was to perform a systematic, prospective evaluation of patients presenting with chilblain-like lesions to characterize this condition occurring during the COVID-19 pandemic.

Methods

Departments dedicated to treating ambulatory and hospitalized patients suspected of having COVID-19 were opened at the Nice University Hospital on March 14, 2020. On April 9, 2020, consultation for skin manifestations suspected to be associated with COVID-19 began. All ambulatory and hospitalized patients with suspected COVID-19 infection referred for consultation were evaluated for chilblain. Patients presenting with chilblain-like lesions underwent thorough clinical, vascular, and laboratory evaluations including white blood cell counts, liver and kidney function, prothrombin time, partial thromboplastin time, erythrocyte sedimentation rate, C-reactive protein levels, D-dimer values, antinuclear antibodies, antiphospholipid antibodies, hemolytic complement (C3, C4, CH50), cryoglobulinemia, parvovirus serology, and interferon-alpha (IFN-α) stimulation and detection. Urine was tested for proteinuria, hematuria, and Leucocyturia. Testing for SARS-CoV-2, using real-time polymerase chain reaction (rt-PCR) on nasopharyngeal swabs, stool samples, and serum serologic analysis, was performed. A skin biopsy was performed at the discretion of the physician. Laboratory and statistical methods are detailed in the eAppendix in the Supplement. The European Centre for Disease Prevention and Control and prevention for COVID-19 case definition and the World Health Organization scale for severity were used.5,6 The institutional review board at the Nice University Hospital independently approved the study. Informed consent was obtained from all patients.

Results

Overall, 40 consecutive outpatients seen between the April 9 and April 17, 2020, were included. No hospitalized patients for COVID-19 presented with chilblain-like lesions. The demographic and clinical characteristics are described in the Table and the eAppendix in the Supplement. The clinical presentation was highly reproducible, with first pruritus and pain of the toes, rarely the heels and fingers, then pink-to-red papules or plaques that evolved to violaceous purpuric lesions with frequent bullous and necrotic evolution (Figure 1, A and B). Acrocyanosis (cyanotic extremities) or cold toes were reported in 19 (47.5%) cases. None of the patients had clinical signs of arterial disease, deep venous thrombosis, or pulmonary embolism.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td>Epidemiologic data</td>
<td></td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>22 (12-67)</td>
</tr>
<tr>
<td>Female sex, No./total No. (%)</td>
<td>21/40 (52.5)</td>
</tr>
<tr>
<td>Contact with patients presenting criteria for possible COVID-19 infection*</td>
<td>24 (60.0)</td>
</tr>
<tr>
<td>Clinical data</td>
<td></td>
</tr>
<tr>
<td>Delays between, median (range), d</td>
<td></td>
</tr>
<tr>
<td>Previous symptoms and onset of chilblain</td>
<td>21 (2-77)</td>
</tr>
<tr>
<td>Onset of chilblain and clinical assessment</td>
<td>14 (3-47)</td>
</tr>
<tr>
<td>Onset of chilblain and last follow-up</td>
<td>27 (18-68)</td>
</tr>
<tr>
<td>Other manifestations at clinical assessment</td>
<td></td>
</tr>
<tr>
<td>Livedo reticularis</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Facial erythema</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Cold toes/acrocyanosis (cyanotic extremities)</td>
<td>19 (47.5)</td>
</tr>
<tr>
<td>Laboratory test results</td>
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<tr>
<td>COVID-19 tests</td>
<td></td>
</tr>
<tr>
<td>Positive rt-PCR (nasopharyngeal and/or stool swabs)</td>
<td>0</td>
</tr>
<tr>
<td>Serologic positive results</td>
<td>12 (30.0)</td>
</tr>
<tr>
<td>Abnormal d-dimers</td>
<td>24 (61.5)</td>
</tr>
<tr>
<td>Positive antinuclear antibodies</td>
<td>9 (22.5)</td>
</tr>
<tr>
<td>Positive antiphospholipid antibodies</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>Abnormal CH50</td>
<td>10 (25)</td>
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<tr>
<td>Cryoglobulinemia, No. positive/tested (%)</td>
<td>0/25</td>
</tr>
<tr>
<td>Parvovirus B19 serology, No. positive/tested (%)</td>
<td>0/33</td>
</tr>
</tbody>
</table>


Twenty-four patients (60%) had contact with possible COVID-19 cases, and 11 (27.5%) met the definition for possible COVID-19 within the 6 weeks preceding the onset of chilblains. The mean duration between suspected COVID-19 clinical signs and the onset of chilblains was 18.5 days. We found 2 chilblain...
family clusters: 2 brothers, and a father and his daughter. In those cases, chilblains occurred within the same period.

Results of SARS-CoV-2 rt-PCR were negative in all cases tested. Real-time PCR was not performed on 14 patients because of absence or excessive delay regarding previous symptoms before the onset of chilblains. Serology was performed in all patients, and 12 (30%) had positive results (IgM positive in 1 patient, IgA positive in 8 patients, and IgG positive in 5 patients) (Table) (eTable 2 in the Supplement).

The most common laboratory anomalies were increased D-dimers in 24 patients (60.0%) with 5 above 500 μg/mL and 2 above 2000 μg/mL. Antinuclear antibodies were noted in 9 patients (22.5%) (only 2 with titer at 1/320) and antiphospholipid antibodies in 4 (10%) with low titer. Results are detailed in the Table and eTables 1 and 2 in the Supplement.

The histopathologic analyses of the 19 skin biopsies showed similar patterns, with 2 main features: lymphocytic inflammation and vascular damage reminiscent of lupus-like chilblain/interferonopathy lesions (Figure 1, C and D). Importantly, interface dermatitis of the intra-epidermal portion of acrosyringium, usually rare in lupus chilblain, was observed in 15 patients (83%) (Figure 1D). In all cases, venular walls appeared mildly thickened, especially in the superficial and reticular dermis (eFigure, A and B in the Supplement). Immunostains demonstrated a proliferation of cells positive for alpha smooth muscle actin (eFigure, C in the Supplement) and negative for endothelial markers (CD34 and CD31) (eFigure, D in the Supplement) evocative of pericyte hyperplasia. In 5 cases, direct immunofluorescence revealed granular deposition of C3 and IgM in the wall of the papillary dermal capillaries and only C3 deposition in all other cases. One case showed an incomplete lupus band with C3 and IgM.

A significant increase of IFN-α production after in vitro stimulation was observed in the chilblain population compared with patients with PCR-positive acute COVID-19 with a range of severity (mild-severe) (Figure 2A). The results did not change when patients were paired for age (Figure 2B). In addition, there was no difference in the IFN-α response of patients with chilblain who developed SARS-CoV-2 antibodies (mean [range], 953.8 [224-2414] pg/mL; median, 765 pg/mL) and those who did not (mean [range], 1132.0 pg/mL [3.3-4086]; median, 765 pg/mL).

The course of chilblains was favorable in all cases, with complete healing of the lesions (n = 40), but 14 patients (35%) had cold toes or acrocyanosis at follow-up (median [range], 27 [18-68] days) (Table) (eTable 1 in the Supplement).

Discussion

In less than 2 weeks, 40 patients presented with chilblains to our dedicated multidisciplinary COVID-19 consultation
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Brief Report Research

Figure 2. Comparison of IFN-α Response in Chilblain Population With Ambulatory and Hospitalized Mild or Severe Cases of Coronavirus Disease 2019 (COVID-19)

A. Interferon alpha (IFN-α) levels after stimulation in the population with chilblains compared with patients with ambulatory or hospitalized mild or severe forms of COVID-19. Results are shown for all the patients tested. The dots represent the level detected for each patient and the bar represents the median. Chilblains: n = 25; median (range) age, 32 (16-38) years; mean (range) IFN-α levels, 751 (224-1468) pg/mL; ambulatory: n = 10; median (range) age, 41 (16-73); mean (range) IFN-α levels, 262 (95.5-1015) pg/mL; hospitalized mild or severe: n = 58; median (range) age, 64 (22-89) years; mean (range) IFN-α levels, 9.8 (1.6-84.9) pg/mL. B. Results when population was paired by age. The dots represent the level of IFN-α detected for each patient and the bar represents the median. Chilblains: n = 25; median (range) age, 32 (16-38) years; mean (range) IFN-α levels, 751 (224-1468) pg/mL; ambulatory: n = 10; median (range) age, 41 (16-73); mean (range) IFN-α levels, 262 (95.5-1015) pg/mL; hospitalized mild or severe: n = 58; median (range) age, 64 (22-89) years; mean (range) IFN-α levels, 89.2 (4.9-777) pg/mL.

The clinical presentation was highly reproducible between patients. Typically, most of these patients were adolescents and young adults without additional medical problems. It is important to stress that the chilblain-like changes resolved in all cases. However, the recovery may be slow because 14 patients (35%) had cold toes or acrocyanosis at a median follow-up of 1 month.

An important finding of this study is that the clinical, biologic, and histologic findings were suggestive of virus-induced type I interferonopathy. Indeed, chilblains are one of the hallmarks of the clinical presentation of genetic type I interferonopathies. Importantly, chilblains observed in type I interferonopathies are known to be sometimes more severe, with bullous lesions and necrosis, as we observed in some of these cases. Type I interferons are crucial in the early response to viral infections, though an inappropriate type I interferon response can contribute to immune pathologies. We observed a significantly higher IFN-α response in the patients with chilblains compared with those with moderate or severe COVID-19. The production of IFN-α is higher in infancy and young adulthood, and then decreases with age. Severe COVID-19 cases, often observed in older populations, are associated with a defect in the type I interferon response leading to uncontrolled proliferation of the virus. Importantly, severe cases of COVID-19 in young men were associated with loss of function variants associated with an altered type I interferon response. This is in accordance with the fact that, to the best of our knowledge, chilblains were never reported in the literature in any of the moderate and severe forms of COVID-19. The exaggerated type I interferon response might also explain the relatively low rate of seropositivity in patients with chilblains because those patients could clear SARS-CoV-2 infection before humoral immunity occurs.

Limitations
The monocentric nature and the absence of cases with rt-PCR testing for SARS-CoV-2 before the onset of the lesions are limitations of this study. The absence of a healthy control group for the IFN-α testing is also a limitation. However, the persistence of the difference between groups when patients are paired by age argues for an unbiased increase response in INFα in the chilblain population.

Conclusions
Taken together, these results demonstrate that chilblain-like lesions observed during the COVID-19 pandemic have characteristics of a viral-induced type I interferonopathy. Although the causative link between SARS-CoV-2 infection and the occur-
ence of chilblain-like lesions still need to be demonstrated, these results suggest that the type of immune response is a key factor explaining the diversity of clinical manifestations observed in COVID-19 infection.

ARTICLE INFORMATION

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Author Affiliations: Department of Dermatology, Université Côte d’Azur, CHU Nice, Nice, France (Hubiche, Le Duff, Seitz-Polski, Giordana, Chiaverini, Giordanengo, Gonfrier, Raimondi, Bausset, Burel-Vandenbos, Dadone-Montaudie); Department of Pathology, Université Côte d’Azur, CHU Nice, Nice, France (Cardot-Leccia, Burel-Vandenbos, Dadone-Montaudie); Department of Immunology, Université Côte d’Azur, UPR O1, URZCA, CHU Nice, Nice, France (Seitz-Polski); Department of Virology, Université Côte d’Azur, UPR O1, URZCA, CHU Nice, Nice, France (Freeman, Burel-Vandenbos, Adjtoutah); Laboratory of Solid Tumors Genetics, Université Côte d’Azur, CHU Nice, Nice, France (Giordanengo, Gonfrier); Université Côte d’Azur, INSERM, U1065, C3M, Nice, France (Giordanengo); Université Côte d’Azur, Cagnes-sur-Mer, France (Raimondi, Bausset, Adjtoutah); Laboratory of Solid Tumors Genetics, Université Côte d’Azur, CHU Nice, Nice, France (Cagnes-sur-Mer, France (Raimondi, Bausset, Adjtoutah)); Institute for Research on Cancer and Aging of Nice (IRCAN), Université Côte d’Azur, CHU Nice, Nice, France (Dadone-Montaudie); Department of Infectiology, Université Côte d’Azur, CHU Nice, Nice, France (Courjon, Mondain); Emergency Department, Université Côte d’Azur, CHU Nice, Nice, France (Contenti); Medical Intensive Care Unit, Université Côte d’Azur, CHU Nice, Nice, France (Cardot-Leccia, Hubiche, Cardot-Leccia).

Author Contributions: Drs Leccia, Hubiche, and Passeron had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Hubiche and Cardot-Leccia contributed equally to the work.

Concept and design: Hubiche, Cardot-Leccia, Bausset, Leftheriotis, Passeron.

Acquisition, analysis, or interpretation of data: Hubiche, Le Duff, Seitz-Polski, Giordana, Chiaverini, Giordanengo, Gonfrier, Raimondi, Bausset, Adjtoutah, Garnier, Burel-Vandenbos, Dadone-Montaudie, Fassbender, Palladini, Courjon, Mondain, Contenti, Dellamonica, Leftheriotis, Passeron.

Drafting of the manuscript: Hubiche, Cardot-Leccia, Le Duff, Giordanengo, Gonfrier, Bausset, Adjtoutah, Garnier, Passeron.

Critical revision of the manuscript for important intellectual content: Hubiche, Cardot-Leccia, Le Duff, Seitz-Polski, Giordana, Chiaverini, Raimondi, Burel-Vandenbos, Dadone-Montaudie, Fassbender, Courjon, Mondain, Contenti, Dellamonica, Leftheriotis, Passeron.

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Supervision: Seitz-Polski, Giordana, Mondain, Contenti, Dellamonica, Leftheriotis, Passeron.

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REFERENCES