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

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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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Supplemental content

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A 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.

Key Points

Question What are the clinical, pathologic, and laboratory characteristics of patients with chilblain-like lesions during the coronavirus 2019 (COVID-19) pandemic?

Findings In this series of 40 consecutive patients with chilblain-like lesions, none had positive findings on polymerase chain reaction (PCR) tests, and 12 (30%) had positive COVID-19 serologic results. Common findings included increased D-dimers, lymphocytic inflammation, vascular damage on skin biopsy results, and a significant interferon-alpha response compared with patients with PCR-positive, acute COVID-19 infection.

Meaning Patients presenting with chilblain-like lesions during the COVID-19 pandemic all had negative PCR results for COVID-19 at the time of the diagnosis and developed antibodies in only 30% of cases, and had histologic and biologic patterns of type I interferonopathy.

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, prothombin 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.

Twenty-four patients (60%) had contact with possible COVID-19 cases, and 11 (27.5%) met the definition for possible

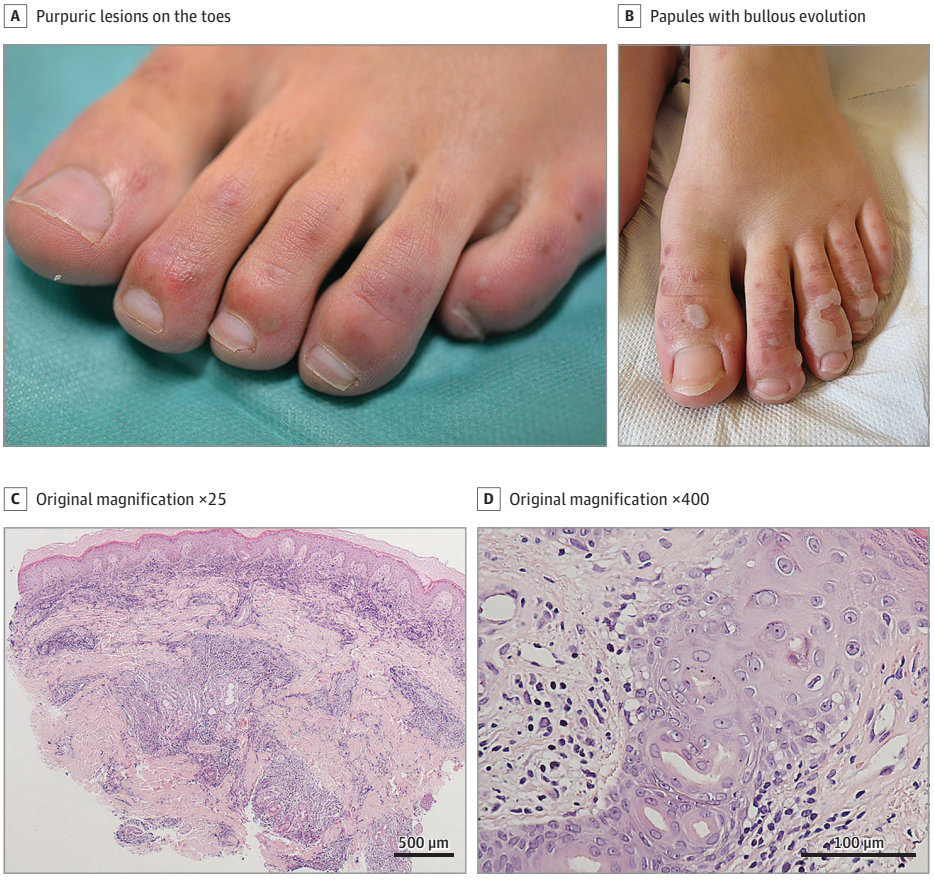
Table. Demographic and Clinical Characteristics of All Patients With Chilblain-like Lesions

Characteristic	No. (%)
Epidemiologic data	
Age, median (range), y	22 (12-67)
Female sex, No./total No. (%)	21/40 (52.5)
Contact with patients presenting criteria for possible COVID-19 infection[a]	24 (60.0)
Patients with criteria for previous possible COVID-19 infection[a]	11 (27.5)
Clinical data	
Delays between, median (range), d	
Previous symptoms and onset of chilblain	21 (2-77)
Onset of chilblain and clinical assessment	14 (3-47)
Onset of chilblain and last follow-up	27 (18-68)
Other manifestations at clinical assessment	
Livedo reticularis	3 (7.5)
Facial erythema	3 (7.5)
Cold toes/acrocyanosis (cyanotic extremities)	19 (47.5)
Laboratory test results	
COVID-19 tests	
Positive rt-PCR (nasopharyngeal and/or stool swabs)	0
Serologic positive results	12 (30.0)
Abnormal d-dimers	24 (61.5)
Positive antinuclear antibodies	9 (22.5)
Positive antiphospholipid antibodies	5 (12.5)
Abnormal CH50	10 (25)
Cryoglobulinemia, No. positive/tested (%)	0/25
Parvovirus B19 serology, No. positive/tested (%)	0/33

Abbreviation: COVID-19, coronavirus disease 2019; rt-PCR, real-time polymerase chain reaction.

[a] European Centre for Disease Prevention and Control Clinical Criteria for Coronavirus Disease 2019.

Figure 1. Clinical and Histologic Presentation of Chilblain-like Lesions



A, Red-to-violaceous purpuric lesions on the toes. Note the bullous and necrotic evolution.
B, Red-to-violaceous papules with marked bullous evolution. C, Dense superficial and deep lymphocytic inflammation with perivascular and peri-eccrine arrangement (hematoxylin-eosin stain).
D, Interface dermatitis extending to the intra-epidermis portion of acrosyringium (hematoxylin-eosin stain).

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).

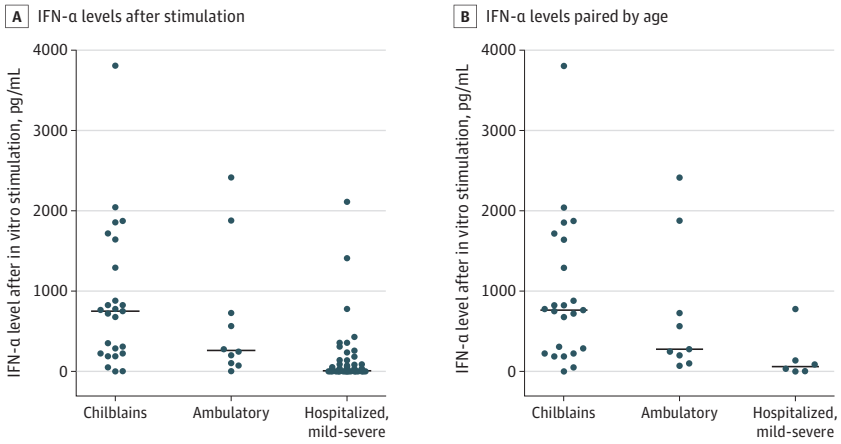
The most common laboratory anomalies were increased D-dimers in 24 patients (60.0%) with 5 above 500 µg/mL and 2 above 2000 µg/mL. Antinuclear antibodies were noted in 9 patients (22.5%) (only 2 with titer at 1/320) and antiphospholipid antibodies in 4 (10%) with low titer. Results are detailed in the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

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) years; mean (range) IFN-α levels, 262 (95.5-1015) pg/mL; hospitalized mild or severe: n; = 7; median (range) age: 42 (22-47) years; mean (range) IFN-α levels, 89.2 (4.9-777) pg/mL.

Discussion

In less than 2 weeks, 40 patients presented with chilblains to our dedicated multidisciplinary COVID-19 consultation clinic. This occurrence is unusual in temperate areas, and corresponded with the spread of SARS-CoV-2 in our region.[7] One-third of patients met clinical criteria for possible COVID-19 infection prior to presentation. Although no patient had positive rt-PCR results, one-third had positive results on serologic analysis. On the basis of these results, definitive proof of a causal link with chilblains and COVID-19 is not demonstrated. However, it is important to emphasize that decreased test sensitivity has been reported in patients with asymptomatic COVID-19 infection, and an alternative immunologic or infectious etiology for these transient chilblain-like lesions was not identified in this cohort.[8,9]

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.[10,11] 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.[12] 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.[13] 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.[14] Importantly, severe cases of COVID-19 in young men were associated with loss of function variants associated with an altered type I interferon response.[15] 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 char-

acteristics of a viral-induced type I interferonopathy. Although the causative link between SARS-CoV-2 infection and the occurrence 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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REFERENCES

1. Galván Casas C, Català A, Carretero Hernández G, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. *Br J Dermatol*. 2020;183(1):71-77.

2. El Hachem M, Diociaiuti A, Concato C, et al. A clinical, histopathological and laboratory study of 19 consecutive Italian paediatric patients with chilblain-like lesions: lights and shadows on the relationship with COVID-19 infection. Published online May 31, 2020. *J Eur Acad Dermatol Venereol*. doi:10.1111/jdv.16682

3. Herman A, Peeters C, Verroken A, et al. Evaluation of chilblains as a manifestation of the COVID-19 pandemic. Published online June 25, 2020. *JAMA Dermatol*. doi:10.1001/jamadermatol.2020.2368

4. Roca-Ginés J, Torres-Navarro I, Sánchez-Arráez J, et al. Assessment of acute acral lesions in a case series of children and adolescents during the COVID-19 pandemic. Published online June 25, 2020. *JAMA Dermatol*. doi:10.1001/jamadermatol.2020.2340

5. Case definition for coronavirus disease 2019 (COVID-19), as of 29 May 2020. European Centre for Disease Prevention and Control. Accessed July 17, 2020. https://www.ecdc.europa.eu/en/covid-19/surveillance/case-definition

6. HO scale for severity of COVID-19 infection. Accessed May 23, 2020. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwjvuJzD48npAhVL0uAKHajJBjMQFjAAegQIBRAB&url=https%3A%2F%2Fwww.who.int%2Fdocs%2Fdefault-source%2Fblue-print%2Fcovid-19-therapeutic-trial-synopsis.pdf%3Fsfvrsn%3D44b83344_1%26download%3Dtrue&usg=AOvVaw3eoPFdtgzO-xJtyYEIxnfx

7. France SP. COVID-19: point épidémiologique en PACA du 16 avril 2020. Accessed May 23, 2020. https://www.santepubliquefrance.fr/regions/provence-alpes-cote-d-azur-et-corse/documents/bulletin-regional/2020/covid-19-point-epidemiologique-en-paca-du-16-avril-2020

8. Deeks JJ, Dinnes J, Takwoingi Y, et al; Cochrane COVID-19 Diagnostic Test Accuracy Group. Antibody tests for identification of current and past infection with SARS-CoV-2. *Cochrane Database Syst Rev*. 2020;6:CD013652 doi:10.1002/14651858.CD013652

9. Long QX, Tang XJ, Shi QL, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat Med*. 2020;26(8):1200-1204. doi:10.1038/s41591-020-0965-6

10. Eleftheriou D, Brogan PA. Genetic interferonopathies: an overview. *Best Pract Res Clin Rheumatol*. 2017;31(4):441-459. doi:10.1016/j.berh.2017.12.002

11. Volpi S, Picco P, Caorsi R, Candotti F, Gattorno M. Type I interferonopathies in pediatric rheumatology. *Pediatr Rheumatol Online J*. 2016;14(1):35. doi:10.1186/s12969-016-0094-4

12. Davidson S, Steiner A, Harapas CR, Masters SL. An update on autoinflammatory diseases: interferonopathies. *Curr Rheumatol Rep*. 2018;20(7):38. doi:10.1007/s11926-018-0748-y

13. McNab F, Mayer-Barber K, Sher A, Wack A, O'Garra A. Type I interferons in infectious disease. *Nat Rev Immunol*. 2015;15(2):87-103. doi:10.1038/nri3787

14. Hadjadj J, Yatim N, Barnabei L, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. [published online ahead of print, 2020 Jul 13]. *Science*. 2020;369(6504):718-724. doi:10.1126/science.abc6027

15. van der Made CI, Simons A, Schuurs-Hoeijmakers J, et al. Presence of genetic variants among young men with severe COVID-19. *JAMA*. 2020;e2013719. doi:10.1001/jama.2020.13719