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Pandemic chilblains: Are they SARS-CoV-2-related or not?

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ABSTRACT

The exact etiopathology of chilblains observed during the Coronavirus Disease 2019 (COVID-19) pandemic is still unclear. Initially, SARS-CoV-2 appeared as the obvious causing agent, but two years of various investigations have failed to convincingly support its direct implication. Most affected individuals have no detectable virus, no anti-SARS-CoV-2 antibodies and no symptoms of COVID-19. Analyses of skin biopsies similarly failed to unambiguously demonstrate presence of the virus or its genome. In a recent hypothesis, SARS-CoV-2 would cause the lesions before being promptly eliminated by unusually strong type I interferon responses. With others, we feel that environmental factors have not been sufficiently considered, in particular cold exposure related to unprecedented containment measures. The cause of pandemic chilblains remains a stimulating puzzle which warrants further investigation.

Chilblain lesions were frequently observed during the Coronavirus Disease 2019 (COVID-19) pandemic [1]. Otherwise healthy adolescents and young adults presented with swollen, erythematous, tender macules and papules and sometimes ulcerations on feet and/or hands. Not surprisingly, SARS-CoV-2 was suspected to cause these lesions. Chilblains are typically cold induced seasonal lesions resulting from vasoconstriction of the deep cutaneous arterioles leading to anoxia, capillary damage and dermal inflammation. Chilblain lesions have also been observed in association with auto-immune disorders or coagulopathy. Chilblains observed during the pandemic do not display a different clinical nor histopathological pattern from the pre-pandemic ones [2,3], except a possibly more severe aspect in the pandemic group. Here, we briefly explain why the pathophysiological link between SARS-CoV-2 infection and these pandemic chilblains is only tenuous and why we [4] and others [5–8] consider that cold exposure associated with lockdown-imposed sedentary lifestyle remains an alternative explanation.

Firstly, the temporal correlation between chilblains and pandemic peaks of COVID-19 raised concerns. The virus was the most likely cause of these chilblains as it was demonstrated to be able to cause lesions in many different tissues, including vessels and skin. Acro-ischemia with cyanosis, livedo reticularis, and gangrene have been observed in severe forms of COVID-19 [9–12]. However, is it really that clear that chilblains are observed when and where COVID-19 cases were more frequent? Actually, chilblains were observed mostly when and where lockdowns were imposed [4–8,13]. Several groups correlated chilblains with lockdown conditions in their respective countries, individual lifestyle changes, clothing conditions, cold exposure of patients, as well as known risk factors of chilblains such as low BMI, history of acrocyanosis or Raynaud syndrome, or positive antinuclear antibodies [4–7,13]. In Nordic countries, no strict lockdown was imposed, and no chilblain outbreaks occurred despite infection rates similar to those of countries reporting chilblains [14]. Chilblains were not observed in tropical countries [15]. In Belgium, we observed chilblain outbreaks during the first and second COVID-19 waves when lockdowns were imposed. However, during the next waves, without lockdowns, reported incidence of chilblains was not higher than during similar seasons of previous years. These epidemiological observations suggest that the increased number of observed lesions could be linked to lockdown-imposed sedentary lifestyles (homeworking or homeschooling) and prolonged barefoot exposure on cold floors in patients with known or unknown risk factors for chilblains.

Secondly, and most importantly, what do we know about the association between SARS-CoV-2 and chilblains at the individual level? Important questions are whether the virus is present in the lesions, whether the affected patients are displaying symptoms of SARS-CoV-2 infection and whether they are carrying the virus.

Patients with chilblains had no or mild symptoms compatible with SARS-CoV-2 infection [3–8,16,17]. RT-qPCR on nasopharyngeal swabs

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and anti-SARS-CoV-2 antibodies were negative in most patient series [18], while anti-SARS-CoV-2 antibodies were positive in a majority of control patients with PCR-confirmed infection [3]. Several groups tried to detect SARS-CoV-2 in chilblains tissue sections using antibodies [19–21]. The results are discordant and point out the insufficient reliability of current immunostainings for SARS-CoV-2 in the skin. RT-PCR on RNA or RNAscope in situ hybridization from chilblain tissue sections did not detect SARS-CoV-2 [4,8,22–24]. Altogether, these data do not convincingly support that SARS-CoV-2 directly causes all pandemic chilblains.

Thirdly, spatial and temporal association of SARS-CoV-2 with chilblains despite virus and antibody undetectability in the affected patients led to a hypothesis involving type I interferons (IFN-I) [25]. The latter are key cytokines at the very early phase of viral infections. Produced by infected cells, they decrease virus production by infected neighboring cells or induce their apoptotic death. Remarkable studies have shown that COVID-19 patients with a decreased IFN-I response, either constitutively or because of anti-IFN auto-antibodies, had more severe clinical courses of the disease [26,27]. For pandemic chilblains, the proposed hypothesis is that some individuals display an unusually strong IFN-I response that (i) eliminates the virus before the appearance of symptoms and of detectable antibody responses and (ii) causes chilblains, like those observed in patients with interferonopathies [28,29]. As attractive as it may be, this hypothesis is not supported by many arguments. Only a few authors have demonstrated systemic elevation of IFN-I and only in a limited number of patients with pandemic chilblains [3,30]. However, there is no reported evidence for higher levels of IFN-I in the blood of patients with pandemic chilblains than in blood of those with seasonal chilblains. Both pandemic and seasonal chilblains were shown to display similar transcriptomic signatures including IFN-I target genes [3] and we did not find higher levels of the IFN-I-induced genes *MX1* and *IRF7* in skin biopsies of pandemic chilblains than in those of pre-pandemic chilblains [23]. If constitutively higher levels of IFN-I were responsible for pandemic chilblains one would expect to observe some of the systemic symptoms described in interferonopathies, as well as family cases. The latter were reported anecdotally, but shared cold exposure could be a confounding factor. Finally, if a strong IFN-I response at the very onset of the infection quickly eliminates the virus, we would not expect to still detect viral proteins weeks later. It follows that if SARS-CoV-2 virions or proteins were confirmed in pandemic chilblain sections, it would not fit with this current IFN-I hypothesis.

Overall, the cause of pandemic chilblains remains a stimulating puzzle. It is impossible to exclude SARS-CoV-2 as the triggering agent of a delayed symptom. It is equally unreasonable to discard the same triggering factor(s) as for classic cold-related chilblains, with an increased incidence and severity during the pandemic period likely due to more chronic and insidious exposure to cold in a large number of patients restricted to unprecedented confinement measures. Genetic polymorphisms as well as SARS-CoV-2-related or other viruses might play a role. To solve the puzzle, which might have more than one answer, we first need better knowledge of the environment of the patients during the weeks preceding chilblains, and undisputable evidence about the presence or absence of SARS-CoV-2 in patients and their affected skin. More sophisticated tools such as spatial transcriptomics or proteomics may confirm hypotheses or open new mechanistic fields.

Authors' contributions

Marie Baeck, Pierre G. Coulie and Axel De Greef performed the literature search; Marie Baeck and Axel De Greef prepared the manuscript; Marie Baeck and Pierre G. Coulie reviewed and approved the manuscript; Marie Baeck, Pierre G. Coulie and Axel De Greef decided to submit the manuscript for publication.

Declaration of Competing Interest

The authors disclosed no financial association or funding source. The authors have no conflict of interest.

References

[1] S.W. Tan, Y.C. Tam, C.C. Oh, Skin manifestations of COVID-19: A worldwide review, JAAD Int. 2 (2021) 119–133, https://doi.org/10.1016/j.jdin.2020.12.003.

[2] J. Kanitakis, C. Lesort, M. Danset, D. Jullien, Chilblain-like acral lesions during the COVID-19 pandemic ("COVID toes"): histologic, immunofluorescence, and immunohistochemical study of 17 cases, J. Am. Acad. Dermatol. 83 (3) (2020) 870–875, https://doi.org/10.1016/j.jaad.2020.05.145.

[3] L. Frumholtz, J.D. Bouaziz, M. Battistella, et al., Type I interferon response and vascular alteration in chilblain-like lesions during the COVID-19 outbreak, Br. J. Dermatol. 185 (6) (2021) 1176–1185, https://doi.org/10.1111/bjd.20707.

[4] A. Herman, C. Peeters, A. Verroken, et al., Evaluation of chilblains as a manifestation of the COVID-19 pandemic, JAMA Dermatol. 156 (9) (2020) 998–1003, https://doi.org/10.1001/jamadermatol.2020.2368.

[5] J. Roca-Ginés, I. Torres-Navarro, J. Sánchez-Arráez, et al., Assessment of acute Acral lesions in a case series of children and adolescents during the COVID-19 pandemic, JAMA Dermatol. 156 (9) (2020) 992–997, https://doi.org/10.1001/jamadermatol.2020.2340.

[6] I. Neri, A. Virdi, I. Corsini, et al., Major cluster of paediatric 'true' primary chilblains during the COVID-19 pandemic: a consequence of lifestyle changes due to lockdown, J. Eur. Acad. Dermatol. Venereol. 34 (11) (2020) 2630–2635, https://doi.org/10.1111/jdv.16751.

[7] J. Rouanet, E. Lang, F. Beltzung, et al., Recent outbreak of chilblain-like lesions is not directly related to SARS-CoV-2 infection, J. Eur. Acad. Dermatol. Venereol. 34 (11) (2020) e689–e692, https://doi.org/10.1111/jdv.16776.

[8] V. Discepolo, A. Catzola, L. Pierri, et al., Bilateral chilblain-like lesions of the toes characterized by microvascular remodeling in adolescents during the COVID-19 pandemic, JAMA Netw. Open 4 (6) (2021), e2111369. Published 2021 Jun 1, https://doi.org/10.1001/jamanetworkopen.2021.11369.

[9] Y. Zhang, W. Cao, M. Xiao, et al., Clinical and coagulation characteristics of 7 patients With critical COVID-2019 pneumonia and acro-ischemia 41 (0) (2020 March 28), E006, https://doi.org/10.3760/cma.j.issn.0253-2727.2020.0006.

[10] C. Magro, J. Mulvey, D. Berlin, et al., Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases, Transl. Res. 220 (2020 Apr 15) 1–13, https://doi.org/10.1016/j.trsl.2020.04.007.

[11] M. Ackermann, S.E. Verleden, M. Kuehnel, et al., Pulmonary vascular Endothelialitis, thrombosis, and angiogenesis in Covid-19, N. Engl. J. Med. 383 (2) (2020) 120–128, https://doi.org/10.1056/NEJMoa2015432.

[12] D. Fernandez-Nieto, J. Jimenez-Cauhe, A. Suarez-Valle, et al., Characterization of acute Acro-ischemic lesions in non-hospitalized patients: a case series of 132 patients during the COVID-19 outbreak, J. Am. Acad. Dermatol. (2020 Apr 24), https://doi.org/10.1016/j.jaad.2020.04.093. S0190-9622(20)30709-X. Online ahead of print.

[13] P.E. McCleskey, B. Zimmerman, A. Lieberman, et al., Epidemiologic analysis of chilblains cohorts before and during the COVID-19 pandemic, JAMA Dermatol. 157 (8) (2021 Aug 1) 947–953, https://doi.org/10.1001/jamadermatol.2021.2120. PMID: 34160569; PMCID: PMC8223123.

[14] N. Kluger, Why are chilblains underreported in Nordic countries during the COVID-19 pandemic? An analysis of Google trends, J. Eur. Acad. Dermatol. Venereol. 35 (2) (2021) e100–e101, https://doi.org/10.1111/jdv.16974.

[15] P. Rerknimitr, C. Theerawattanawit, P. Lertpichitkul, et al., Skin manifestations in COVID-19: the tropics experience, J. Dermatol. 47 (12) (2020 Dec) e444–e446, https://doi.org/10.1111/1346-8138.15567. Epub 2020 Sep 2. PMID: 32881043.

[16] E.E. Freeman, D.E. McMahon, J.B. Lipoff, et al., Pernio-like skin lesions associated with COVID-19: A case series of 318 patients from 8 countries, J. Am. Acad. Dermatol. 83 (2) (2020) 486–492, https://doi.org/10.1016/j.jaad.2020.05.109.

[17] L. Le Cleach, L. Dousset, H. Assier, et al., Most chilblains observed during the COVID-19 outbreak occur in patients who are negative for COVID-19 on polymerase chain reaction and serology testing, Br. J. Dermatol. 183 (5) (2020) 866–874, https://doi.org/10.1111/bjd.19377.

[18] V. Sánchez-García, R. Hernández-Quiles, E. de Miguel-Balsa, A. Docampo-Simón, I. Belinchón-Romero, J.M. Ramos-Rincón, Are the chilblain-like lesions observed during the COVID-19 pandemic due to severe acute respiratory syndrome coronavirus 2? Systematic review and meta-analysis, J. Eur. Acad. Dermatol. Venereol. 36 (1) (2022) 24–38, https://doi.org/10.1111/jdv.17672.

[19] C.J. Ko, M. Harigopal, W. Damsky, et al., Perniosis during the COVID-19 pandemic: negative anti-SARS-CoV-2 immunohistochemistry in six patients and comparison to perniosis before the emergence of SARS-CoV-2, J. Cutan. Pathol. 47 (11) (2020 Nov) 997–1002, https://doi.org/10.1111/cup.13830. Epub 2020 Sep 9. PMID: 32745281; PMCID: PMC7436569.

[20] I. Colmenero, C. Santonja, M. Alonso-Riaño, et al., SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven paediatric cases, Br. J. Dermatol. 183 (4) (2020 Oct) 729–737, https://doi.org/10.1111/bjd.19327. Epub 2020 Aug 5. PMID: 32562567; PMCID: PMC7323219.

[21] C. Santonja, F. Heras, L. Núñez, L. Requena, COVID-19 chilblain-like lesion: immunohistochemical demonstration of SARS-CoV-2 spike protein in blood vessel endothelium and sweat gland epithelium in a polymerase chain reaction-negative

patient, Br. J. Dermatol. 183 (4) (2020) 778–780, https://doi.org/10.1111/bjd.19338.
[22] G. Battesti, J. El Khalifa, N. Abdelhedi, et al., New insights in COVID-19-associated chilblains: A comparative study with chilblain lupus erythematosus, J. Am. Acad. Dermatol. 83 (4) (2020) 1219–1222, https://doi.org/10.1016/j.jaad.2020.06.1018.
[23] A. De Greef, M. Choteau, A. Herman, et al., Chilblains observed during the COVID-19 pandemic cannot be distinguished from the classic, cold-related chilblains, Accepted for publication in Eur. J. Dermatol. (January 2022). In press.
[24] E. Robustelli Test, P. Sena, A.G. Locatelli, et al., RNAscope in situ hybridization and RT-PCR for detection of SARS-CoV-2 in chilblain-like lesions: A clinical, laboratory and histopathological study, Pediatr. Dermatol. 39 (1) (2022) 77–83, https://doi.org/10.1111/pde.14903.
[25] D. Lipsker, A chilblain epidemic during the COVID-19 pandemic. A sign of natural resistance to SARS-CoV-2? Med. Hypotheses 144 (2020) 109959, https://doi.org/10.1016/j.mehy.2020.109959.
[26] P. Bastard, L.B. Rosen, Q. Zhang, et al., Autoantibodies against type I IFNs in patients with life-threatening COVID-19, Science. 370 (6515) (2020), eabd4585, https://doi.org/10.1126/science.abd4585.
[27] Q. Zhang, P. Bastard, Z. Liu, et al., Inborn errors of type I IFN immunity in patients with life-threatening COVID-19, Science. 370 (6515) (2020), eabd4570, https://doi.org/10.1126/science.abd4570.
[28] M.P. Rodero, Y.J. Crow, Type I interferon-mediated monogenic autoinflammation: the type I interferonopathies, a conceptual overview, J. Exp. Med. 213 (12) (2016) 2527–2538, https://doi.org/10.1084/jem.20161596.
[29] R. Papa, S. Volpi, M. Gattorno, Monogenetic causes of chilblains, panniculitis and vasculopathy: the type I interferonopathies, G. Ital. Dermatol. Venereol. 155 (5) (2020) 590–598, https://doi.org/10.23736/S0392-0488.20.06709-7.
[30] T. Hubiche, N. Cardot-Leccia, F. Le Duff, et al., Clinical, laboratory, and interferon-alpha response characteristics of patients with chilblain-like lesions during the COVID-19 pandemic, JAMA Dermatol. 157 (2) (2021) 202–206, https://doi.org/10.1001/jamadermatol.2020.4324.