Research letter

Pernio and early SARS-CoV-2 variants: natural history of a prospective cohort and the role of interferon

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Dear Editor, Since the start of the pandemic, reports of pernio have paralleled rising cases of COVID-19 globally. Individuals with pandemic-associated pernio have frequently reported close contacts with known or suspected SARS-CoV-2 infection and variable COVID-19 symptoms themselves.[1] However, direct evidence of this relationship has been limited due to low rates of viral detection [by nasopharyngeal polymerase chain reaction (PCR)], seroconversion, and SARS-CoV-2-specific T-cell immunity.[2] We and others have suggested that an effective antiviral response involving elevated interferon (IFN) production, mirroring pernio in the monogenic type 1 interferonopathies, might underlie this phenomenon and produce an abortive seronegative infection, obscuring the SARS-CoV-2 footprint.[3,4] Here we describe the natural history of pandemic-associated pernio in our cohort and explore its association with SARS-CoV-2, providing potential insight into the disease mechanism.

Patients diagnosed with pernio (onset in or after March 2020) by dermatologists at our institution were considered for inclusion in this prospective cohort study, which was approved by the institutional review board. Exclusion criteria included previous diagnosis of systemic lupus erythematosus or chilblain lupus. Seventy-nine patients in Wisconsin were enrolled from April 2020 to February 2022. Patients were followed longitudinally via phone calls, electronic correspondence and patient surveys to capture demographic information, medical history and clinical features of pernio. SARS-CoV-2 PCR and serology results were included when available.

Affected participants were young (median age 16 years, range 2–59) and predominately white (87%) and female (56%). Pandemic-associated pernio affected the feet in 74 patients (94%), with red–purple discoloration often with pruritus or pain (41 of 51, 80%). Discoloration lasted a median duration of 8 weeks. Eleven patients (14%) reported extracutaneous symptoms ≤ 4 weeks preceding pernio onset, including upper respiratory and occasionally systemic symptoms for a median of 8 days (range 1–35). While most patients were otherwise healthy, a few had a history of sporadic pernio (6%). Autoimmune diseases (9%) were enriched in the cohort relative to the general population (~3%) and included inflammatory bowel disease, rheumatoid arthritis, juvenile idiopathic arthritis, and mixed connective tissue disease.[5]

Twenty-two patients (28%) reported exposure to confirmed or suspected COVID-19 infection a median of 3 weeks prior to onset of pernio (range 0–17 weeks). Of those tested, three of 50 (6%) had a positive PCR test, with pernio onset a median of 1 week later. Most tests were performed after pernio onset and may have failed to detect the virus if it was cleared quickly. Two of 44 (5%) patients were positive for SARS-CoV-2 nucleocapsid IgG antibodies a median of 6 weeks after pernio onset. Of those tested for total SARS-CoV-2 spike IgG/IgA/IgM antibodies, only two patients, both previously PCR positive, mounted antibody responses (two of 43, 5%).

Recurrences were common in our cohort. Of the 58 patients who provided follow-up information, 30 (52%) reported relapse, which is similar to previous studies.[6,7] Eighteen patients indicated more than one recurrence, with a median of two recurrences per person. Among those who received the COVID-19 vaccine, five of 46 reported episodes closely following vaccination (onset ranging from 0 to 3 weeks), supporting a vaccine-triggered phenomenon. These episodes occurred following primary (Johnson & Johnson, n = 1), secondary (Pfizer, n = 1; Moderna, n = 1) and booster (Pfizer, n = 3) vaccine doses.

New-onset pernio and recurrences tightly aligned with the trends in mean monthly COVID-19 positivity rate in Wisconsin (Figure 1). Importantly, most occurred when the mean monthly ambient temperature dropped below 9 °C. Yet despite ongoing recruitment efforts and continued recurrences, there was a paucity of enrolment from March to December 2021. We suspect this may reflect a phenomenon that is dependent on both variant and temperature. COVID-19 infections waned in Wisconsin from March 2021 through the early summer. Delta subsequently surged between August and October 2021, when the median monthly temperature was 13–23 °C, above the speculated threshold of most cases. Omicron arrived in December 2021, when the temperature plunged to a mean of −0·7 °C. Omicron is associated with milder disease severity on the population level in part due to enhanced angiotensin-converting enzyme 2-mediated entry properties, which largely limit SARS-CoV-2 to the upper airways.[8]

We hypothesize that confinement to the upper airways facilitates priming of the lungs with type I interferon (IFN-I), reducing viral replication elsewhere and decreasing the global systemic IFN-I response, which are requisite for the

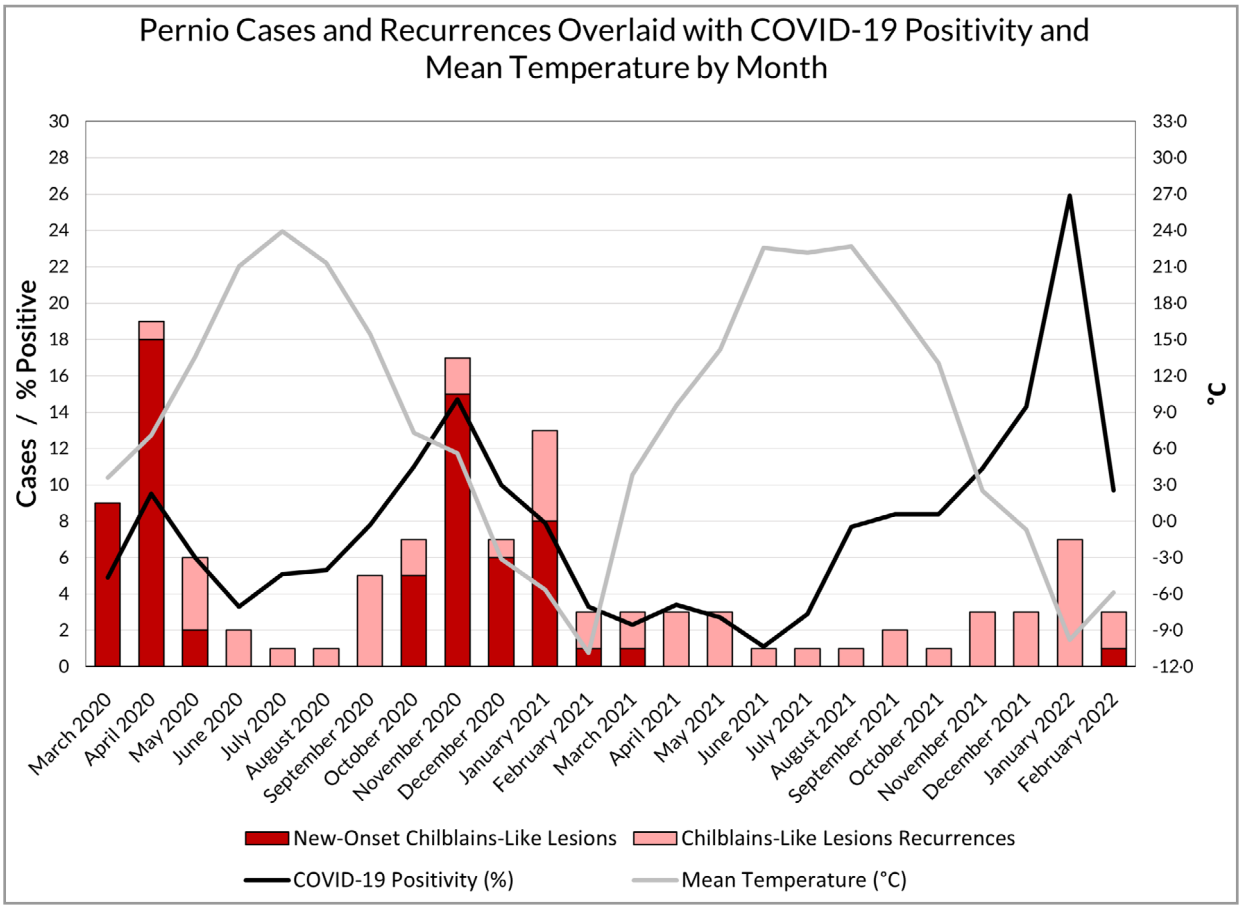

Figure 1 Cases of new-onset pernio and recurrences in our cohort align tightly with trends in mean 7-day COVID-19 positivity in Wisconsin and mean temperature in Madison, Wisconsin by month.

development of pernio. Yet the mechanism of IFN induction in pernio remains poorly understood. Although pernio is a hallmark manifestation of the interferonopathies, systemic treatment with IFN-I is insufficient for its development.

In our cohort, enrichment with IFN-mediated autoimmune disorders supports the role of IFNs in pandemic-associated pernio. Close alignment with cold and propensity for relapses suggest a durable immune memory response. Ongoing translational investigation in this cohort will help to precisely elucidate the role of IFN-I, along with the genetic and immunological mechanisms that underlie pandemic-associated pernio.

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References

1 Freeman EE, McMahon DE, Lipoff JB *et al.* Pernio-like skin lesions associated with COVID-19: a case series of 318 patients from 8 countries. *J Am Acad Dermatol* 2020; **83**:486–92.

2 Gehlhausen JR, Little AJ, Ko CJ *et al*. Lack of association between pandemic chilblains and SARS-CoV-2 infection. *Proc Natl Acad Sci U S A* 2022; **119**:e2122090119.
3 Hubiche T, Cardot-Leccia N, Le Duff F *et al*. Clinical, laboratory, and interferon-alpha response characteristics of patients with chilblain-like lesions during the COVID-19 pandemic. *JAMA Dermatol* 2021; **157**:202–6.
4 Frumholtz L, Bouaziz JD, Battistella M *et al*. Type I interferon response and vascular alteration in chilblain-like lesions during the COVID-19 outbreak. *Br J Dermatol* 2021; **185**:1176–85.
5 Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. *Autoimmun Rev* 2003; **2**:119–25.
6 Moghadam P, Frumholtz L, Jaume L *et al*. Frequency of relapse and persistent cutaneous symptoms after a first episode of chilblain-like lesion during the COVID-19 pandemic. *J Eur Acad Dermatol Venereol* 2021; **35**:e566–8.
7 Freeman EE, McMahon DE, Lipoff JB *et al*. Cold and COVID: recurrent pernio during the COVID-19 pandemic. *Br J Dermatol* 2021; **185**:214–16.
8 Sigal A. Milder disease with Omicron: is it the virus or the pre-existing immunity? *Nat Rev Immunol* 2022; **22**:69–71.

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Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.