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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Full list of author affiliations.

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Cold and COVID: recurrent pernio during the COVID-19 pandemic

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Dear Editor, Pernio is a commonly reported cutaneous manifestation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1] Our international registry of COVID-19 dermatological manifestations has collected 1176 total cases of COVID-19 skin manifestations, including 619 cases of pernio in patients with suspected or confirmed COVID-19.[1] Most patients with new-onset pernio were entered into the registry after the first pandemic wave (79% in March to May 2020). Starting in September 2020, the registry received reports of a subset of these patients who developed recurrent pernio in the following months. Herein, we present the cases of the first 18 patients with recurrent pernio in the COVID-19 dermatology registry. Patients with a prior pre-pandemic history of pernio were excluded. The registry was reviewed by the Partners Healthcare Institutional Review Board and was determined to not meet the definition of Human Subjects Research.

These patients with recurrent pernio (n = 18) had a median age of 22 years [interquartile range (IQR) 16–37], were 72% male, and 83% white. Patients resided in the USA (n = 16) [Massachusetts (n = 7), California (n = 3), Pennsylvania (n = 2), New York (n = 1), Rhode Island (n = 1), Connecticut (n = 1) and Michigan (n = 1)], the Netherlands (n = 1) and the UK (n = 1). Patients were SARS-CoV-2 polymerase chain reaction (PCR) and antibody positive (6%), antibody-positive only (11%), PCR-positive only (17%), close contacts of a laboratory-confirmed case (17%) or clinically suspected only (50%).

Of note, patient 2 was SARS-CoV-2 antibody-positive 5 weeks after initial pernio lesions started, but tested negative twice for SARS-CoV-2 PCR including a few days after both initial pernio and recurrent pernio symptoms began. Conversely, patient 4 tested PCR positive for SARS-CoV-2 shortly after COVID-19 symptoms of anosmia, dysgeusia and myalgia began, but when antibody testing became available several months later, tested antibody negative. These cases highlight the importance of the timing of testing, and also highlight how patients even with documented prior COVID-19 may test negative on commercial antibody tests.

Overall, 17 of 18 patients initially developed pernio during March to May 2020, the first wave of the COVID-19 pandemic in the USA and Europe (northern hemisphere spring). The pernio resolved in May–July and recurred between September and December 2020 in autumn/winter (Figure 1). The exception (patient 6) was symptomatic with PCR-confirmed COVID-19 in August, developed pernio in September that remitted by October, and then recurred in November 2020.

These cases of recurrent pernio suggest that cold temperatures, combined with a history of SARS-CoV-2 infection, may prompt and perpetuate the inflammatory response.[2] Recent data have demonstrated that patients with pernio/chilblains in the setting of acute SARS-CoV-2 infection have high interferon-alpha responses,[2,3] which may allow rapid control of SARS-CoV-2. Furthermore, not only are there similarities between patients with pernio and type I interferonopathies,[3] but cold exposure has also been noted to cause pernio flares in patients with type I interferonopathies.[4] In cases of recurrent pernio, the mechanism is not yet clear. It remains to be seen whether initial SARS-CoV-2 infection primes patients to be more cold sensitive and therefore prone to recurrent pernio, or whether cold temperature itself is triggering some type of secondary interferon-alpha response without a new SARS-CoV-2 infection.[5]

Limitations to this case series include that only one-third of patients had laboratory confirmation of SARS-CoV-2 infection, an effect heightened by lack of SARS-CoV-2 laboratory testing during the first wave and also noted by prior studies.[1,6,7] In patients without laboratory-confirmed disease, recurrent pernio/chilblains during the pandemic may also be because of an unrelated cause. However, none of these patients experienced pernio pre-pandemic. This finding also highlights the possibility that other cases of recurrent perniosis prior to the COVID-19 pandemic could have been triggered by viral infection.

We do not yet know how frequently, and for how long, patients who developed pernio in the setting of the COVID-19 pandemic will experience recurrent symptoms with subsequent cold exposure. Reports have noted 'long-hauler' cutaneous manifestations of COVID-19,[8] and it remains to be seen how persistent and/or recurrent post-COVID pernio will be. Future studies on recurrent pernio may enhance our

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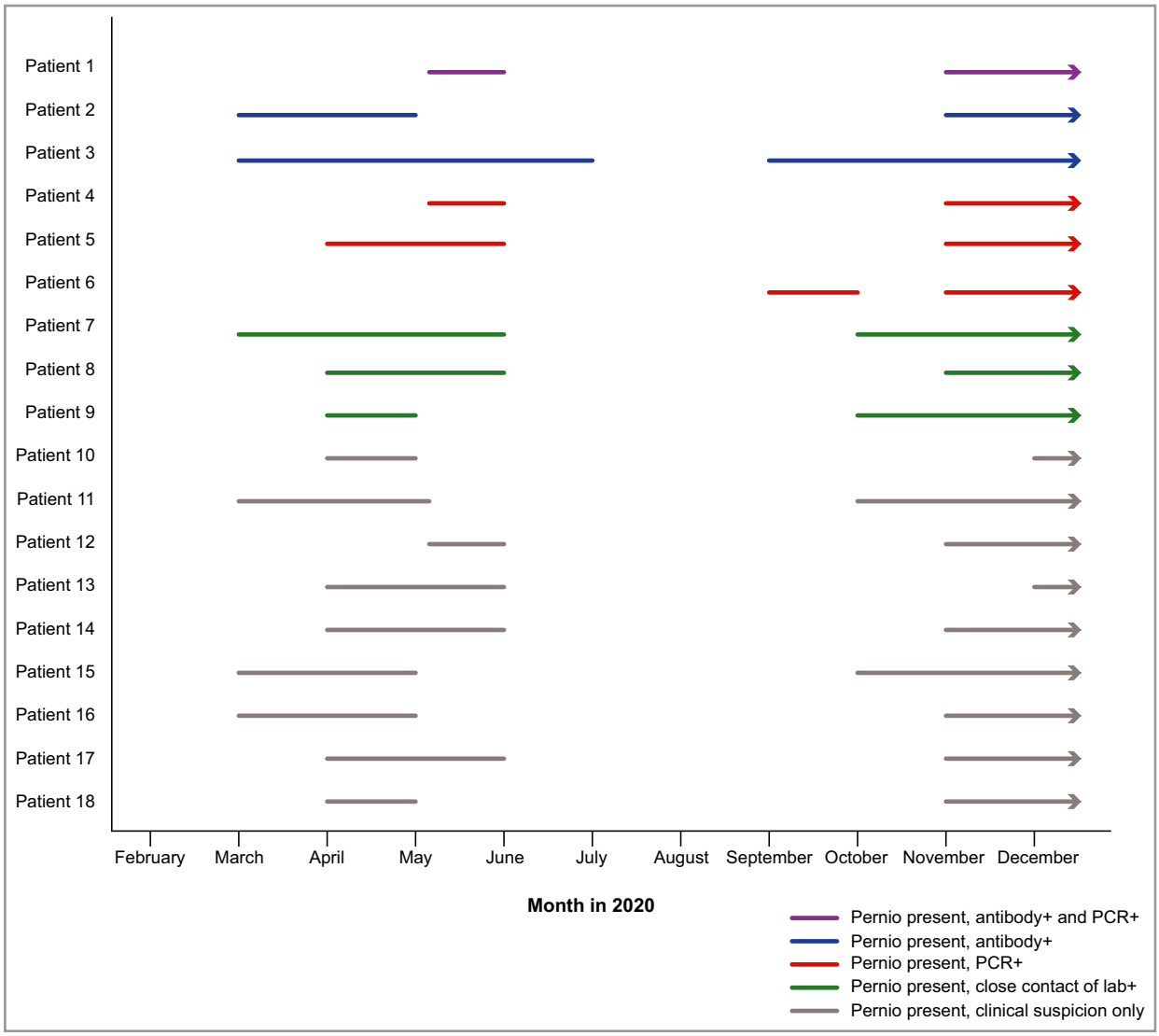

Figure 1 Timeline demonstrating 18 patients who experienced pernio during two discrete timepoints in the setting of laboratory-confirmed or suspected COVID-19 infection during 2020. PCR, polymerase chain reaction; +, positive.

understanding of the role of temperature and interferon, as well as best practices for patient management.

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Oral clindamycin and rifampicin in the treatment of hidradenitis suppurativa–acne inversa in patients of paediatric age: a pilot prospective study

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Dear Editor, Hidradenitis suppurativa–acne inversa (HS–AI) is a chronic, inflammatory, recurrent, debilitating skin disease of the terminal hair follicle that usually presents with painful, deep-seated, inflamed lesions in the apocrine-gland-bearing areas of the body.[1] The disease typically occurs in the second and third decade of life, but early onset in patients of paediatric age (age 0–16 years) has been reported in 2–8·1% of cases.[2,3] No therapeutic trials have been published in paediatric HS–AI, and treatment recommendations are based on case reports and extrapolation from adult studies.[1]

In adults, several cases have been reported that described the beneficial effect of combination therapy using clindamycin 300 mg twice daily with rifampicin 600 mg once daily or 300 mg twice daily for up to 10 weeks.[4–7] Although no randomized controlled trial has been conducted, the results of the published case series are consistent and support the use of this combination. None of the published series include any paediatric patients, but both drugs are used in children to treat other infections, suggesting that this may also be a viable approach to treating paediatric HS–AI.

We performed a prospective, noncomparative study, enrolling 20 patients aged ≤ 16 years who were affected by active inflammatory HS–AI, to assess the efficacy and the tolerability of a 10-week combination of oral clindamycin (600 mg daily) and rifampicin (600 mg daily). As all patients enrolled weighed ≥ 50 kg, the adult dosage was prescribed. No restrictions regarding previous treatments were established.

The parameters used to evaluate the efficacy of the treatment were (i) severity of the HS–AI, assessed using the Sartorius score at baseline (T0) and after 10 weeks of treatment (T1), and (ii) the number of exacerbations during the treatment compared with those that occurred in the previous 3 months. Exacerbations were defined as acute development of at least one wide inflammatory lesion. Patients were considered responders if they achieved a Sartorius score improvement > 25%. The patients were informed that after the end of the antibiotic treatment, a relapse of HS–AI was possible. Finally, adverse events and their causal relationship to medications were assessed.

For the comparisons between the groups relating to continuous variables, nonparametric tests (Wilcoxon signed-rank test) were used. $P < 0·05$ was considered statistically significant. The main clinicodemographic data are summarized in Table 1. The body mass index (BMI) of the patients was calculated as BMI-for-age and was expressed as a percentile.[8] Four of 20 patients enrolled (20%) had a normal weight, four patients (20%) were overweight and 12 patients (60%) were obese. All 20 patients completed the 10-week treatment and had a mean Sartorius score of 59·6 (range 12·0–176·0) at T0 and 28·0 (range 7·0–80·0) at T1, corresponding to a mean

Table 1 Main clinicodemographic data of the studied patients

Number of patients	20
Sex, n (%)	
Male	8 (49)
Female	12 (60)
Mean age (years)	15·05
Range (SD)	10–16 (2·20)
Mean age of onset (years)	11·63
Range (SD)	6–16 (3·14)
Mean age at diagnosis (years)	13·85
Range (SD)	9–16 (2·34)
Mean duration of disease (years)	3·42
Range (SD)	0–6 (1·64)
Hurley stage, n (%)	
I	5 (25)
II	11 (55)
III	4 (20)
Mean BMI (kg m^2) for age percentile[a]	88·10
Range (SD)	23–97 (18·82)
BMI-for-age weight status, n (%)	
Underweight[b]	0 (0)
Normal weight[b]	4 (20)
Overweight[b]	4 (20)
Obese[b]	12 (60)
Current smokers, n (%)	4 (20)
Family history, n (%)	4 (20)

[a]The body mass index (BMI)-for-age percentile growth charts are the most commonly used indicator to measure the size and growth patterns of children and teens (from age 2–20 years).[8]
[b]BMI-for-age weight status categories and the corresponding percentiles are as follows: less than the 5th percentile (underweight); ≥ 5th percentile to less than the 85th percentile (normal or healthy weight); ≥ 85th to less than the 95th percentile (overweight) and ≥ 95th percentile (obese).[8]

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