




ORIGINAL ARTICLES

Acral changes in pediatric patients during COVID 19 pandemic: Registry report from the COVID 19 Response Task Force of the Society of Pediatric Dermatology (SPD) and Pediatric Dermatology Research Alliance (PeDRA)

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Abstract

Background/Objective: In spring 2020, high numbers of children presented with acral pernio-like skin rashes, concurrent with the coronavirus disease 2019 (COVID-19) pandemic. Understanding their clinical characteristics/ infection status may provide prognostic information and facilitate decisions about management.

Methods: A pediatric-specific dermatology registry was created by the Pediatric Dermatology COVID-19 Response Task Force of the Society for Pediatric Dermatology (SPD) and Pediatric Dermatology Research Alliance (PeDRA) and was managed by Children's Hospital of Philadelphia using REDCap.

Results: Data from 378 children 0-18 years entered into the registry between April 13 and July 17, 2020 were analyzed. Data were drawn from a standardized questionnaire completed by clinicians which asked for demographics, description of acral lesions, symptoms before and after acral changes, COVID-19 positive contacts, treatment, duration of skin changes, laboratory testing including SARS-CoV-2 PCR and antibody testing, as well as histopathology. 229 (60.6%) were male with mean age of 13.0 years (\pm 3.6 years). Six (1.6%) tested positive for SARS-CoV-2. Pedal lesions (often with pruritus and/or pain) were present in 96%. 30% (114/378) had COVID-19 symptoms during the 30 days prior to presentation. Most (69%) had no other symptoms and an uneventful course with complete recovery.

Conclusions and Relevance: Children with acral pernio-like changes were healthy and all recovered with no short-term sequelae. We believe these acral changes are not just a temporal epiphenomenon of shelter in place during the spring months of

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the first wave of the COVID-19 pandemic and may be a late phase reaction that needs further study.

KEYWORDS

exanthems, infection-viral, skin signs of systemic disease

1 | INTRODUCTION

Perniosis is characterized by inflammation of small vessels, in association with cold exposure.¹⁻³ The incidence in children is estimated at 2.5 cases/million children per year though this number comes from small studies.¹ In spring 2020, increased frequency of acral changes resembling pernio emerged as a possible cutaneous manifestation of coronavirus disease 2019 (COVID-19).³⁻⁶ Prior reports show male adolescent/ young adult predominance with mild/no preceding viral symptoms and largely negative SARS-CoV-2 testing.^{4,5,7}

When initial cases of COVID-19 with SARS-CoV-2 PCR positivity were reported in Wuhan, China, 2.4% of these cases were children with a mean age of 7 years, of whom 56% were males. In the initial cohort, children generally had mild disease (90%), with a median duration of symptoms of 2 days.⁸⁻¹⁰ With the assumption of mild disease in pediatric patients and limited testing availability in early 2020, children were tested less frequently than adults even when they had symptoms or positive contacts.^{11,12} When COVID-related skin changes were first noted, acral areas of erythema were described. Acral changes affected younger adults (average age 32.5 years), occurred after other symptoms (59%), persisted for days to weeks (mean 12.7 days), and generally were associated with milder disease (no hospital admission or need for intensive care). In one Spanish study, 41% of pernio cases (29/71) had SARS-CoV-2 confirmed.⁵ More recent studies of the acral rash, however, mostly show negative nasopharyngeal PCR testing for SARS-CoV-2 or were unable to correlate due to lack of any testing in those with acral skin changes.^{6,13}

This pediatric-specific registry describes a large cohort of children with acral changes. We aimed to discover if pediatric-specific trends in demographics, clinical features, laboratory findings, and histopathology would lead to better understanding of this phenomenon in relationship to SARS-CoV-2.

2 | METHODS

A pediatric-specific registry to collect information from healthcare professionals in the United States, Canada, United Kingdom, and Central America (primarily pediatric dermatologists, pediatricians, and pediatric rheumatologists) was established April 12, 2020 by the Pediatric Dermatology SARS-CoV-2 Response Task Force, a collaborative effort by members of the Society for Pediatric Dermatology (SPD) and Pediatric Dermatology Research Alliance (PeDRA). The registry is housed by Children's Hospital of Philadelphia REDCap (Research Electronic Data Capture, Vanderbilt University, Nashville,

TN). Healthcare providers were notified about the registry via the SPD, PeDRA, and the British Society for Paediatric Dermatology (BSPD). The registry captured demographics, past medical history, family history, clinical findings and course, treatment, viral PCR/antibody testing, histologic evaluation, and other laboratory testing. The data were analyzed using Stat-16 software (StatCorp, College Station, TX). The registry was granted an exemption from the Children's Hospital of Philadelphia Institutional Review Board after determination that it did not meet the definition of Human Subjects Research. Each submitting site's data entry was regulated and approved or waived by the local institution's IRB.

3 | RESULTS

The registry compiled 384 individual cases of patients with acral skin changes between April 13, 2020 and July 17, 2020. Six subjects were excluded due to age greater than 18 years, and 378 (age 2 months to 18 years, mean 13 years \pm 3.6 years) were evaluated (Table 1). Most were male (60.6%) and white/Caucasian (72%) (Table 1). Most lived in the United States (69.6%) or Canada (23.3%), with the majority in the United States from California (22.5%), Illinois (11.1%), Wisconsin (6.6%), and New York (2.4%), New Jersey (4.8%) and Pennsylvania (3.8%). 309/378 (81.7%) patients had no comorbidities.

Approximately 30% (114/378) had COVID illness symptoms during the 30 days prior to presentation, including fever (12.7%; 48/378) and dry cough (11.6%; 44/378) (Table 2). Potential exposure to SARS-CoV-2 prior to the acral changes was noted by 33.6% (127/378), most often by those living in a community with high rates (16.7%; 63/378) or contact with a family member exposed through work (7.7%; 29/378). Close contact with a SARS-CoV-2-positive individual was reported by 2.6% (10/378) (Table 2).

Of 378 subjects, 1.6% had SARS-CoV-2 infection confirmed by PCR or antibody testing, while 134 (35.4%) had negative testing for the virus by PCR or tested negative for antibodies (8). 47.4% confirmed they had no SARS-CoV-2 testing. None were hospitalized or died. Some subjects (~35%) had additional blood testing. Among these subjects, abnormalities were demonstrated in complete blood counts, antinuclear (typically speckled) and anti-phospholipid antibodies, complement, D-dimer, fibrinogen, and inflammatory markers (Table 3).

The lesions lasted an average of 21.6 days and were virtually always on the feet (96.3%). Some subjects also had lesions on the hands (11.9%) or head/neck (11.4%) (Table 2 and Supplemental Table S1). Toes were most commonly affected, but changes on the dorsal feet, heels, and periungual area were also reported. The skin changes were

TABLE 1 Demographics (N = 378)

Characteristic	Value
Sex assigned at birth, n (%)	
Male	229 (60.6)
Female	148 (39.1)
Unknown/Not reported	1 (0.3)
Age, mean (range)	13.0 (0.17-18.0)
Race, n (%)	
White/Caucasian	272 (72.0)
Asian	43 (11.4)
Unknown/Not reported	43 (11.4)
More than one	11 (2.9)
Black or African American	7 (1.9)
American Indian or Alaska Native	2 (0.5)
Native Hawaiian or Other Pacific Islander	0 (0.0)
Ethnicity, n (%)	
Non-Hispanic or Latino	277 (73.3)
Unknown/Not reported	82 (21.7)
Hispanic or Latino	19 (5.0)
Country, n (%)	
United States	257 (68.0)
Canada	88 (23.3)
UK	21 (5.6)
Unknown/Not reported	7 (1.8)
Ireland	2 (0.5)
Argentina	2 (0.5)
Kuwait	1 (0.3)
US State, n (%)	
California	83 (32.3)
Illinois	42 (16.3)
Wisconsin	24 (9.3)
Unknown/Not reported	23 (8.9)
New Jersey	15 (5.8)
Pennsylvania	13 (5.1)
Massachusetts	12 (4.7)
Minnesota	9 (3.5)
New York	9 (3.5)
New Hampshire	5 (1.9)
Utah	5 (1.9)
Georgia	4 (1.6)
Colorado	2 (0.8)
Indiana	2 (0.8)
Michigan	2 (0.8)
Vermont	2 (0.8)
Delaware	1 (0.4)
Maine	1 (0.4)
Maryland	1 (0.4)
Ohio	1 (0.4)
Virginia	1 (0.4)

TABLE 2 Symptom characteristics and duration (N = 378)

Characteristic	Value
COVID-19 Symptoms 30 days before, n (%)	
Yes	114 (30.2)
No	261 (69.0)
Unknown/Not reported	3 (0.08)
Symptoms before rash, n (%)	
Fever	48 (12.7)
Other	46 (12.2)
Dry cough	44 (11.6)
Rhinorrhea	32 (8.5)
Sore throat	25 (6.6)
Malaise	18 (4.8)
Abdominal	16 (4.2)
Myalgia	10 (2.6)
Anosmia	2 (0.5)
Other mucous	2 (0.5)
Chest pain	1 (0.3)
Irritability	1 (0.3)
Ulcers	1 (0.3)
Duration of COVID symptoms (non-skin), n (%)	
0-7 days	70 (18.5)
8-14 days	25 (6.6)
15-30 days	14 (3.7)
More than 30 days	9 (2.4)
Did not have COVID non-skin symptoms	248 (65.6)
Unknown/Not reported	12 (3.2)
Duration of acral eruption n (days)	
Average	21.6
Standard Dev	28.9
Median	14.0

largely described as pink or red macules/patches (91.3%), bullae (6.1%), vesicles (11.6%), erosions (14.8%), and ulcers (3.7%). In 5.3% (20/378), desquamation was noted. Thirteen cases had associated histopathology. Among these, the most common changes were a superficial and deep lymphocytic infiltrate with vacuolar change and purpura as well as hemorrhagic parakeratosis in the stratum corneum (Table S2).

4 | DISCUSSION

We present a large collection of children and adolescents with acral skin manifestations that presented in the initial phases of the SARS-CoV-2 pandemic. Although most cases were in adolescent males, several cases occurred in infants (youngest just 2 months of age). The age and male predominance noted here are atypical for classical pernio, but similar to reports in primarily adult COVID registries.^{2,3}

We hypothesized a connection between SARS-Cov-2 exposure/infection and these changes but found it difficult to confirm

TABLE 3 Known exposures and testing (N = 378)

Characteristic	Value
Exposure 30 days Before, n (%)	
Yes	127 (33.6)
No	247 (65.3)
Unknown/Not reported	4 (1.1)
Exposure Type, n (%) ^a	
Lives in community with high positive cases	63 (16.7)
Exposure to family/personal contact healthcare worker	29 (7.7)
Travel to area with high COVID cases	21 (5.6)
Close contact with presumed COVID	20 (5.3)
Close contact with positive COVID	10 (2.6)
COVID-19 Diagnosis, n (%)	
Unknown	225 (59.5)
COVID testing not performed/not reported	225 (59.5)
Negative	134 (35.4)
Negative COVID test	134 (35.4)
Positive	19 (5.0)
Presumptive based on symptoms	13 (3.4)
Positive COVID test (PCR)	4 (1.1)
Positive COVID test (Antibody)	2 (0.5)
Optional additional blood tests, n (%)	
ANA	
Normal	49 (13.0)
High	34 (9.0)
Low	0 (0.0)
Anti-phospholipid antibodies	
Normal	50 (13.2)
High	1 (0.3)
Low	0 (0.0)
Complete blood count with differential	
Normal WBC	86 (22.8)
High WBC	21 (5.6)
Low WBC	9 (2.4)
Complement (C3/C4/CH50)	
Normal	57 (15.1)
High	11 (2.9)
Low	5 (1.3)
D-dimer and Fibrinogen	
Normal	69 (18.3)
High	6 (1.6)
Low	6 (1.6)

^a16 patients had a combination of multiple exposures.

causation because of limited testing for the virus/antibodies and the striking proportion of negative results in children who did have testing. Notably, there is growing evidence that SARS-CoV-2 PCR initially had high false negative rates (2%-29%) making early tests

not reliable to exclude infection.^{12,14} Second, there is no reference standard for measuring sensitivity of SARS-CoV-2 antibodies in asymptomatic/mild cases making it harder to exclude a connection only on these grounds.¹⁴

Among the 6 patients confirmed to have SARS-Cov-2 by PCR or antibodies, most had acral changes weeks (average 22 days) after the initial SARS-CoV-2 symptoms or positive test suggesting that the skin inflammation may represent a late manifestation or post-viral change triggered by a secondary inflammatory response. In these cases, inflammation and a dysregulated immune response resulting from even mild SARS-CoV-2 infection might prompt those with environmental insults (cold damp environments) or genetic predisposition to manifest with new skin changes (Figure 1).

We could then hypothesize that if the skin changes are a result of late inflammation, RT-PCR testing will be negative in most because testing at the time of the rash is too late to capture the initial infection. Traditional diagnostic and current antibody testing may be missing those with antibodies against the spike protein. Recent data support this hypothesis. In one study, immunohistochemistry for SARS-CoV/SARS-CoV-2 spike protein showed granular positivity in endothelial cells and epithelial cells of eccrine glands in two acral biopsies in patients with minimal or no systemic symptoms.¹⁵ Magro et al found endothelial cell localization of SARS-CoV-2 protein in three cases of COVID-19-associated perniosis and Colmenero showed SARS-CoV-2 RNA in skin biopsy samples from patients who previously had negative nasopharyngeal PCR testing.^{6,13}

Still, there is no agreement. A few argue that pernio is solely the result of greater exposure (such as by being barefoot in unheated homes) during the period of sheltering in place.^{16,17} We disagree with this because there has been no evidence of unseasonably cold and wet weather that would explain the higher incidence of pernio observed.¹⁸ In a retrospective study of 3.2 million children in Chicago, 8 cases of pernio were identified in a 10-year period compared to 41 identified in Chicago in the spring of 2020.¹ The Children's Hospital of Philadelphia saw an average of 2.6 cases of pernio a year annually from 2015 to 2019, compared to 17 cases in April-May 2020. Analysis of weather data from Philadelphia shows that 2020 was not statistically colder (or warmer), nor did it have more precipitation during these months than over the same months during the previous 5 years. Still, many children reported doing schoolwork at desks or tables without socks or shoes, which would be unusual in the school environment.¹⁹ Despite this, there is no evidence that home schooling or bare feet can explain the male adolescent predominance or why infants/toddlers would have increased numbers of cases.^{18,19}

The second wave of increased acral pernio cases many reported in the early fall underscores a direct relationship to the virus rather than a temporal coincidence. Since our first analysis, 56 additional cases were added to the registry in the late summer, fall, and winter and mostly similar trends were observed with slightly higher rates of positive testing. Of these 56 cases, 5 tested positive by PCR for SARS-CoV-2 (Supplemental Table S3). One subject was hospitalized due to COVID-19. We also reached out to those who had submitted cases in our first analysis regarding recurrences. Several



FIGURE 1 (A) Photograph showing erythema on the tips of the toes as well as some desquamation on the 2nd toe and periungual redness. (B) Photograph of registry participant with purple and red macules on the heel. (C) Photograph of participant who had acral changes in March 2020 and then again in the fall of 2020 showing red patches with erosions on the toes including periungual region

investigators and clinicians noted recurrences of acral pernio in the fall and winter in subjects previously submitted. In one subject, acral pernio recurred, and the subject tested negative for SARS-CoV-2 antibodies after the recurrence.

Most subjects were Caucasian, despite ethnically diverse locations. Possible reasons for this include the following: i) difficulty in recognizing subtle erythema in darker skin; and ii) poorer access for skin of color populations to telemedicine during lockdown periods.^{20,21} This is particularly relevant given increased risk of severe [COVID-19] disease and MIS-C (Multi-Inflammatory Syndrome) in children of color.^{22,23}

Blood testing was performed in 35% of subjects, and some children with few or no other symptoms had laboratory abnormalities. Positive antinuclear antibody (ANA) titers (titer > 1:80) were found in 34/83 (41%), with no other comorbidities, symptoms, or autoimmune family history. Positive ANA can be a marker for acute and chronic infection.^{24,25} Here, of those positive, many had speckled patterns and one was eventually diagnosed with Sjogren disease (reinforcing the need to consider autoimmune disease in children with pseudo-chilblains).²⁵ Other potential evidence of recent/active infection/inflammation (despite negative testing for SARS-CoV-2) was elevation in levels of hemoglobin, complement, and interferon gamma. There are reports of adults and children with severe presentations of COVID-19 with ischemic purpura and sequelae due to coagulation abnormalities.¹³ In this registry, few children had laboratory testing and none had histopathologic evidence of clotting abnormalities, consistent with milder disease/good prognosis. Among those with coagulation abnormalities, there were no complications, necrosis, or poor outcomes. Our findings suggest additional blood tests should be considered. Those with positive ANAs should be rechecked to understand the relationship between this marker and SARS-CoV-2 infection. Providers may also consider SARS-CoV-2 antibody testing in children who have positive ANA testing and acral symptoms but have not undergone prior SARS-CoV-2 testing.

In summary, our large dataset of children presenting with acral pernio-like lesions during the COVID-19 pandemic suggests there could be a direct, not just temporal, relationship with SARS-CoV-2. Despite only 1% of the cases having positive PCR testing for SARS-CoV-2, our findings provide possible support for an association between pernio-like changes and SARS-CoV-2. Reasons include the

large number of cases studied ($n = 378$), the number (30.2%) with viral symptoms prior to skin changes, and some patients with a known exposure to COVID-19, as well as many with inflammatory marker elevations. Though an epiphenomenon of the pandemic and a byproduct of quarantine are possible, we believe this is unlikely. Definitive, reproducible confirmation of a direct association between SARS-CoV-2 infection and acral pernio-like changes in large numbers of patients has remained elusive, likely in part due to the availability of and access to reliable and specific viral tests both clinically and histologically. The interim analysis of this database may provide those directly involved in the care of children—clinicians, families/caregivers, health policy makers, and public health officials—with a better sense of prognosis for children who present with pernio-like lesions, since all recovered without short-term serious sequelae. Further studies are necessary to explain knowledge gaps, in particular the low rates of positive SARS-COV-2 tests and the precise immunopathogenesis of this cutaneous finding relative to infection and immunity.

We were limited by selection and confirmation bias. At the time of data collection, SARS-COV-2 diagnostic testing was not widespread and even currently available testing may be inadequate. Media exposure to the idea of “COVID toes” likely introduced recruitment bias. Differences in the ability to recognize acral changes in dark skin tones and/or decreased access to care may explain why few Black patients were added to registry. Prospective studies with improved antibody-based immunoassays, diagnostic lesional PCR, and inflammatory biomarkers are needed. Longitudinal studies would help to determine long-term sequelae. In the short term, it appears that patients with acral changes had full recovery.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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