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# Clustered cases of acral perniosis: Clinical features, histopathology, and relationship to COVID-19

Kelly M. Cordoro MD[1] | Sean D. Reynolds MD[1] | Rachel Wattier MD[2] | Timothy H. McCalmont MD[3]

[1]Department of Dermatology and Pediatrics, University of California San Francisco, Benioff Children's Hospital, San Francisco, CA, USA

[2]Department of Pediatrics, Division of Infectious Diseases and Global Health, University of California San Francisco, Benioff Children's Hospital, San Francisco, CA, USA

[3]Department of Dermatology and Pathology, University of California San Francisco, San Francisco, CA, USA

**Correspondence**
Kelly M. Cordoro, MD, Professor of Dermatology and Pediatrics, Department of Dermatology, University of California, San Francisco, 1701 Divisadero Street, 3rd floor, San Francisco, CA 94115, USA.
Email: Kelly.Cordoro@ucsf.edu

## Abstract

**Background/Objectives:** A recent marked increase in pediatric and adult patients presenting with purpuric acral lesions concerning for ischemia, thrombosis and necrosis has been observed in COVID-19 prevalent regions worldwide. The clinical and histopathological features and relationship to COVID-19 have not been well described. The objective of this case series is to describe the clinical features and determine the histopathologic findings and clinical implications of the clusters of acral perniosis cases identified in pediatric patients.

**Methods:** We describe six otherwise healthy adolescents—three siblings per family from two unrelated families—presented within a 48-hour period in April, 2020, with acral perniosis-like lesions in the context of over 30 similar patients who were evaluated within the same week.

**Results:** Affected patients had mild symptoms of viral upper respiratory infection (URI) or contact with symptomatic persons 1-2 weeks preceding the rash. They all presented with red to violaceous macules and dusky, purpuric plaques scattered on the mid and distal aspects of the toes. Skin biopsies performed on each of the six patients demonstrated near identical histopathologic findings to those of idiopathic perniosis, with a lymphocytic inflammatory infiltrate without evidence of thromboembolism or immune complex vasculitis. While SARS-CoV-2 polymerase chain reaction was negative, testing was performed 1-2 weeks after URI symptoms or sick contact exposure.

**Conclusion:** We offer a clinical approach to evaluation of patients with this presentation and discuss the possibility that these skin findings represent a convalescent-phase cutaneous reaction to SARS-CoV-2 infection.

## 1 | INTRODUCTION

Background: There has been a significant increase in outpatient cases of acral purpura concerning for ischemia, thrombosis and necrosis in COVID-19 prevalent regions internationally and in the U.S.[1] In early April, our center saw a sharp uptick in pediatric patients with itchy, tender acral lesions. The temporal relationship between suggestive viral symptoms in affected patients and/or close contacts and the appearance of the lesions suggest a relationship to SARS-CoV-2 infection. A report detailing acro-ischemia in the context of acquired hypercoagulable states in critically ill COVID-19 patients from Wuhan describes cyanosis, bullae, and gangrene of the digits. Four of these patients developed disseminated intravascular coagulation (DIC) and five died.[2] In addition, adult patients with COVID-19 with coagulopathy, antiphospholipid antibodies, and multiple infarcts have been described.[3] Whether a relationship exists between

  

the severe adult inpatient cases and systemically healthy pediatric patients with acral purpura is unknown. We present a detailed investigation of the clinical and histopathological features of six healthy adolescent outpatients presenting with acral purpura amidst the COVID-10 pandemic. We offer an approach to evaluation, discuss the likelihood that these skin findings represent a convalescent-phase cutaneous reaction to SARS-CoV-2 infection, and offer evidence that pediatric cases are distinct from the severe ischemic and thrombotic cases in adults.

## 2 | CASES

We report six patients—three siblings per family from two unrelated families—who presented to our tertiary referral academic children's hospital in Northern California within a 48-hour period in early April 2020. The patients ranged in age from 12 to 17 years; five were male, one female. All were healthy with no significant past medical history nor family history of inflammatory, autoimmune genetic or coagulopathic conditions. Provisional diagnoses prior to dermatology evaluation included post-infectious vasculitis, perniosis, coagulopathy, and septic emboli. There were striking similarities in their histories and presentations. Two siblings from one family reported rhinorrhea, congestion, sore throat, and subjective fevers 1 week prior to the onset of skin lesions. No symptoms were noted by the third sibling nor the three siblings from the other family. None of the patients had cough, shortness of breath, or changes in their sense of smell or taste. All six patients had contact with adults who had mild, transient upper respiratory infection (URI) symptoms 1 to 2 weeks prior to the onset of skin lesions. None of the patients had known contact with confirmed COVID-19 cases. Each of the three siblings from one family reported international travel to Europe, Africa, and Hawaii 3 weeks prior to development of skin lesions. Notably, all patients developed acral skin lesions within one week of each other (within each family). Nearly all described the lesions as itchy and a few reported tenderness in the context of swelling. None experienced Raynaud's phenomenon, arthralgias, or myalgias. All live in Northern California where the temperatures ranged from 45 to 76°F in the 3 weeks prior to presentation, with monthly average lows and highs of 49°F and 63°F, respectively, for this time of year. Rainfall in the month before presentation was 1.36 inches, below the usual monthly average of 1.46 inches.[4]

## 3 | PHYSICAL FINDINGS

Physical examination revealed healthy-appearing adolescents with normal vital signs and similar cutaneous morphology (Figure 1). All had red to violaceous macules and dusky, purpuric plaques scattered on the mid and distal aspects of the toes. More severely affected digits were edematous with overlying superficial bullae and focal hemorrhagic crust. None of the digits appeared ischemic or necrotic. Several patients had scattered petechial and purpuric macules on the heels, soles and distal aspect of the dorsal feet, and a prominent distribution along the lateral foot. A few had subtle erythematous macules around the distal nail folds. Half had livedo reticularis (reticulated erythema) involving the flexor surfaces of the forearms, the dorsal hands, and the dorsal feet. None had other relevant oral, ocular, skin, hair, or nail findings.

## 4 | LABORATORY FINDINGS

Comprehensive evaluations including complete blood count (CBC) with differential, autoimmune and coagulopathy panels, markers of inflammation, comprehensive metabolic panels, and urinalysis revealed no significant alterations in any of the patients. One patient had an elevated ASO and DNAse B in the context of a recent positive pharyngeal culture for group A *Streptococcus*. Interestingly, each of the siblings from one family had very subtle, isolated reductions in fibrinogen with no other abnormalities. All were SARS-CoV-2 polymerase chain reaction (PCR) negative by pooled nasopharynx and oropharynx swabs; COVID-19 IgM and IgG antibodies were negative; however, there are concerns regarding the validity of serologic testing (discussed below).

## 5 | HISTOPATHOLOGIC FINDINGS

We obtained two biopsies of lesional skin from all six patients for conventional and direct immunofluorescence (DIF) microscopy (Figure 2). Routine sections demonstrated a superficial and deep lymphocytic infiltrate that also abuts the junctional zone, where vacuolar change and purpura were noted. Hemorrhagic parakeratosis was found in the stratum corneum. The dermal infiltrate was tightly perivascular and also perieccrine, and intramural lymphocytes ("lymphocytic vasculitis") were present in the thin muscular walls of small vessels. No evidence of thrombosis was found in the vessels. Direct immunofluorescence was negative for immunoreactant deposition in all cases. Overall, the histopathologic findings were nearly identical in all patients and to those seen in perniosis.

## 6 | DISCUSSION

The cases reported herein describe the clinical presentation, laboratory evaluation, and histopathologic findings of a cluster of pediatric patients with perniosis during the COVID-19 pandemic. The temperatures have not been unseasonably cold nor damp in our area and none of the patients have a history of perniosis. The temporal relationship to the pandemic indicates that perniosis could be a cutaneous sign of SARS-CoV-2 infection. Perniosis, also called chilblains, is a cold-induced inflammatory vasculopathy. Patients are typically healthy though perniosis-like lesions have been described in patients with coagulopathy, hematologic malignancy, autoimmune, and hereditary conditions.[5] Primary perniosis is typically a seasonal

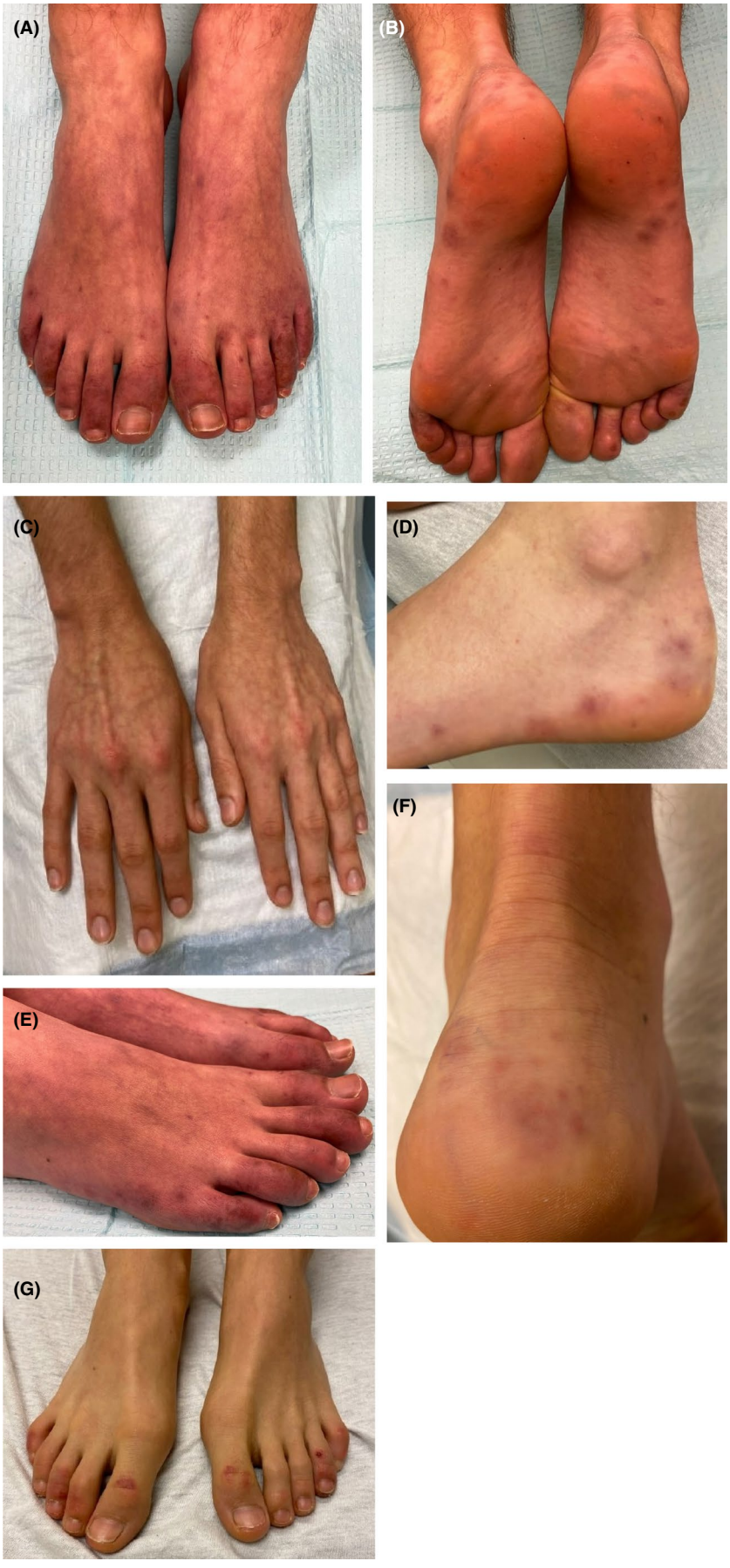


**FIGURE 1** Clinical features of acral perniosis in two adolescent patients: dusky purpuric patches on the dorsal toes (A, E and G) with focal lesions on the dorsum of the foot and clustered along Wallace's line and heels (A, B, D, E and F). Net-like vascular pattern (livedo reticularis) on the dorsal hands and feet (A, C and E)

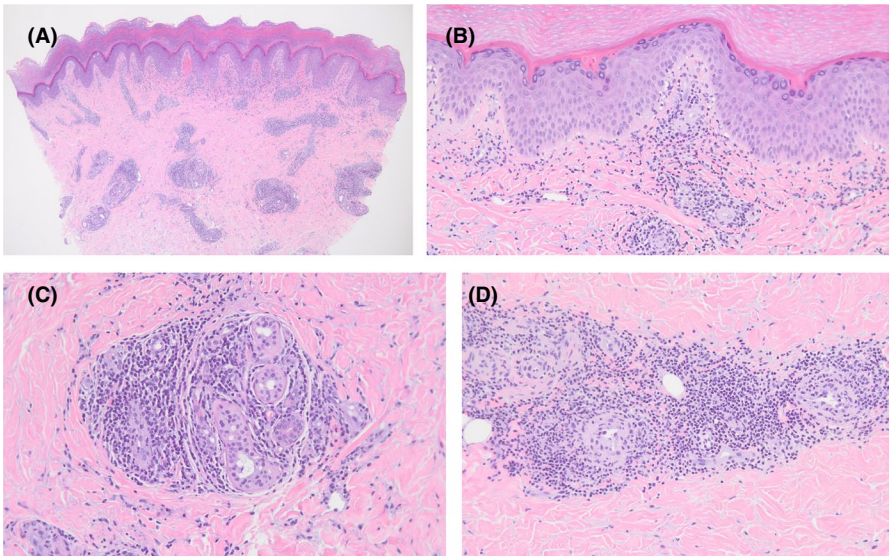


**FIGURE 2** Histopathologic sections show a superficial and deep lymphocytic infiltrate (A) that is both perivascular and perieccrine in distribution (B–D). In the perivascular component of the infiltrate, some lymphocytes are present in the walls of small vessels (C and D). There are also perijunctional lymphocytes with vacuolar change (B). Mucin deposition can be seen in both the reticular and periadnexal dermis (B–D)

condition that presents initially with erythema and swelling of the digits upon exposure to cool, damp conditions followed by red-purple purpuric patches and papules on the dorsal digits. The changes are thought to result from vasoconstriction and vasospasm leading to anoxia and vascular damage.[6] Peripheral skin changes including acrocyanosis and livedo reticularis are commonly observed. Primary perniosis often improves with conservative care including warming measures (wearing insulated clothing, gloves, and footwear), topical corticosteroids, and non-steroidal anti-inflammatory medications. Additional therapies may be required in severe cases.

## 7 | CLINICAL IMPLICATIONS AND RELEVANCE TO THE COVID-19 PANDEMIC

While clusters of perniosis cases have been reported in Australia[7] and parts of China[8] during unusually cold periods, perniosis has also clustered in association with viral and bacterial infection including *Mycoplasma*.[7] Cold agglutinins and cryoglobulins produced in response to viral infection have been hypothesized as a cause of post-infectious perniosis.[9] Laboratory evaluation and histopathology of our cases did not show evidence of cryproteinemia or other coagulopathy and suggest the etiology is inflammatory but not thromboembolic. Evidence from Wuhan and early US investigations in children suggest that a majority of COVID-19 infected children are mildly symptomatic.[10] Effective innate immune responses to viral infection rely on type I interferons (IFNs) which activate the JAK-STAT signaling pathway leading to the expression of genes that block viral replication and dissemination.[11] Interestingly, patients with Type I interferonopathies have similar immune signaling and develop perniosis-type lesions.[12,13] It is possible that healthy children have a robust initial IFN-1 immune response to infection that produces transient cold-like symptoms (as described in our patients) or no symptoms at all, and which may both protect from progressive infection and precipitate inflammatory perniosis. It seems unlikely that the perniosis observed in healthy outpatients has a direct relationship to the severe coagulopathy, ischemic necrosis and infarcts observed in critically ill adult patients with COVID-19 infection.[2]

To date, widespread SARS-CoV-2 testing has not been performed on healthy pediatric outpatients and therefore the timing of the infection relative to onset of perniosis is unclear. The timeline of our cases suggests that acral perniosis may represent a response to subclinical infection or a convalescent-phase reaction. Given the uncertain relationship to SARS-CoV-2 and the as-yet unclear natural history of these cases, patients who are otherwise well and systemically asymptomatic could be watched closely and offered conservative care measures. Those who are febrile, have severe, diffuse or necrotic skin lesions or systemic symptoms should undergo comprehensive laboratory evaluation including coagulation panels and possibly skin biopsy to clarify the diagnosis and direct management. Patients presenting with acral perniosis should be tested for COVID-19 with PCR and antibodies if available given the clinical and epidemiologic implications.

Of note, 24 additional cases evaluated in the Bay Area last week were in adolescent patients aged 10 to 19 years. Thirteen of 24 of these have been tested with upper respiratory PCR and all have been SARS-CoV-2 negative. Lack of positive testing has presented obstacles to defining the precise relationship between acral perniosis and SARS-CoV-2 infection. It is important to note limitations in testing for COVID-19, particularly later in the course of illness. False-negative PCR testing has been reported from multiple upper respiratory sites and false-negative rates may be higher in minimally symptomatic persons.[14] Viral detection in the upper respiratory tract is highest in the pre-symptomatic and early symptomatic phases of infection and declines before day 5 of respiratory symptoms.[15,16] Antibody testing for COVID-19 is very newly developed at this time. It is unclear what the ideal timing of testing should be, and concerns have arisen about clinical validity and reproducibility of the current commercially available tests.[17] It is also possible that recent cases of acral perniosis are unrelated to SARS-CoV-2 infection directly and instead represent a temporally associated epiphenomenon that is not yet fully understood. Some have hypothesized that

acral perniosis is quarantine-related due to prolonged barefoot exposure to cool indoors. Assessment of a large sample size over time will clarify the demographics, range of clinical features and severity, association with COVID-19 (as antibody testing becomes more reliable and widely available) and provide data for risk stratification in terms of evaluation, management, and clinical course. The Pediatric Dermatology Research Alliance COVID-19 Response Task Force has developed a registry to rapidly collect and analyze cases to gain a better understanding of this phenomenon.[18]

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## ORCID

*Kelly M. Cordoro* https://orcid.org/0000-0001-9158-2111
*Sean D. Reynolds* https://orcid.org/0000-0003-3760-3676

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