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From Your Nose to Your Toes: A Review of Severe Acute Respiratory Syndrome Coronavirus 2 Pandemic–Associated Pernio

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Despite thousands of reported patients with pandemic-associated pernio, low rates of seroconversion and PCR positivity have defied causative linkage to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Pernio in uninfected children is associated with monogenic disorders of excessive IFN-1 immunity, whereas severe COVID-19 pneumonia can result from insufficient IFN-1. Moreover, SARS-CoV-2 spike protein and robust IFN-1 response are seen in the skin of patients with pandemic-associated pernio, suggesting an excessive innate immune skin response to SARS-CoV-2. Understanding the pathophysiology of this phenomenon may elucidate the host mechanisms that drive a resilient immune response to SARS-CoV-2 and could produce relevant therapeutic targets.

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INTRODUCTION

In March 2020, just weeks after the onset of community spread of COVID-19 in Italy, reports of pandemic-associated pernio emerged. Shortly thereafter, dermatologists in the United States were inundated with pernio referrals as the first surge of COVID-19 arrived in the United States (Bouaziz et al., 2020; Cordoro et al., 2020; Duong et al., 2020; Galván Casas et al., 2020; Landa et al., 2020; López-Robles et al., 2020; Piccolo et al., 2020). The phenotype of cool extremities with pain/swelling followed by red–violaceous discoloration and finally vesiculation of the toes and fingers were strikingly consistent (Figure 1a). Whereas older age was an important risk factor for severe infection, most patients with pernio were young, with a median age of 25 years in an international dermatology registry (Castelo-Soccio et al., 2021; Freeman et al., 2020). Many had close contact with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected individuals; yet, nearly all were otherwise healthy and denied typical respiratory manifestations of COVID-19 (Castelo-Soccio et al., 2021; Freeman et al., 2020). The spatial and temporal association between pernio and the COVID-19 pandemic has now been independently observed across multiple countries, including Italy, Spain, Germany, the United Kingdom, France, and the United States.

The strength of this spatial and temporal association along with its consistency across multiple countries supports a SARS-CoV-2–triggered phenomenon. Yet, low rates of positive PCR testing of nasopharyngeal samples (0–20%) and antibody positivity (0–55%) across 175 publications and thousands of reported patients have led some authors to suggest that this is an epiphenomenon (Baeck and Herman, 2021; Galván Casas et al., 2020). This review will summarize and integrate the growing evidence for a causal relationship with SARS-CoV-2 and construct a mechanistic hypothesis. Pandemic-associated pernio augments the knowledge regarding the spectrum of SARS-CoV-2 infection and reinforces the critical importance of IFN-1 signaling in disease outcomes. A robust IFN-1 response in patients who remain asymptomatic and antibody negative could suggest a population with intrinsic resistance to severe COVID-19. Because the host immune response to SARS-CoV-2 infection is a critical determinant for COVID-19 outcomes, understanding those with natural resiliency to SARS-CoV-2 exposure could produce clinically relevant therapeutic targets.

INBORN ERRORS OF IFN-1 AND LIFE-THREATENING INFECTION

IFN-1 responses are tightly regulated to ensure protective immunity while avoiding toxicity from excessive and prolonged IFN signaling. They are largely produced in the blood by plasmacytoid dendritic cells (pDCs) in response to viral

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Abbreviations: ACE2, angiotensin-converting enzyme 2; HCV, hepatitis C virus; pDC, plasmacytoid dendritic cell; RAS, renin-angiotensin system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

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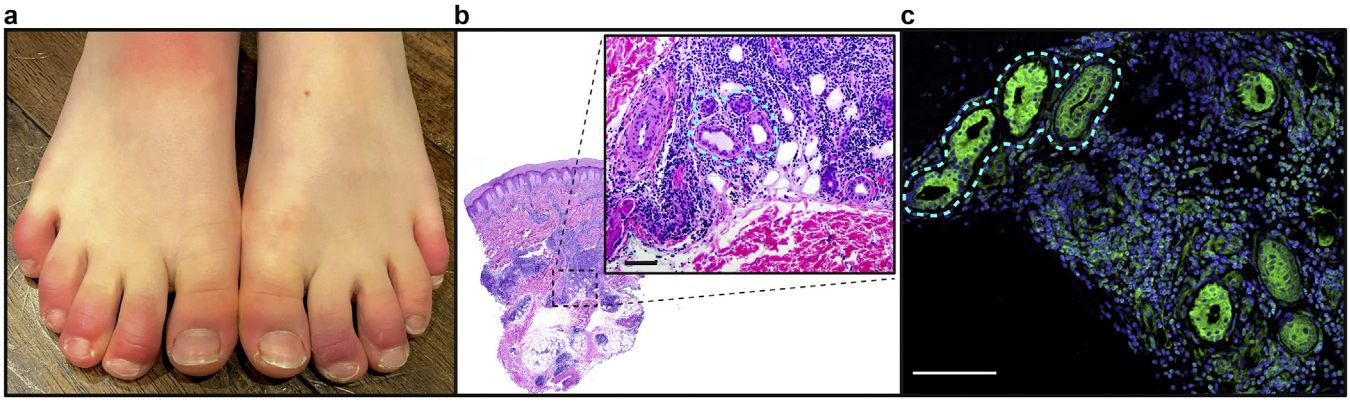

Figure 1. Pandemic-associated pernio presentation and histopathology. (**a**) Representative clinical photographs of COVID toes, with red–violaceous discoloration and swelling on multiple distal digits bilaterally. (**b, c**) Representative histopathologic section of a patient's punch biopsy specimen (H&E); (**b**) demonstrating dense perivascular and periadnexal inflammatory infiltrate; (inset) magnification demonstrating tight inflammation around eccrine structures (outlined). Bar = 100 μM. (**c**) Staining of eccrine structures (outlined) for ACE2 (green) and nuclei (blue). Bar = 100 μM. ACE2, angiotensin-converting enzyme 2.

infection through the activation of toll-like receptors 3, 7, and 9; RIG-I; and MDA5. IFN-1 is produced in lower amounts by >400 discernable cell types (intrinsic immunity). On binding to IFN-1 receptor, the IFN-1 (13 IFN-α, IFN-β, IFN-ε, IFN- κ, IFN-ω) activates robust antiviral defense programs of INF-stimulated genes, which obstruct various steps of viral replication. Monogenic variants that impair key IFN-1–related genes are associated with life-threatening infections due to influenza pneumonia, respiratory syncytial virus, rhinovirus, and herpes encephalitis (Asgari et al., 2017; Ciancanelli et al., 2015; Lamborn et al., 2017; Zhang et al., 2007).

IFN-1 SIGNALING IS CRITICAL IN COVID-19 OUTCOMES

Recent investigations of host-specific responses to SARS-CoV-2 have confirmed the central role of IFN-1 signaling in COVID-19 outcomes. An attenuated IFN-1 response was found in critically ill patients with SARS-CoV-1 (Channappanavar et al., 2016). In an international cohort, our team found that 3% of patients with life-threatening COVID-19 harbor loss-of-function variants involved in IFN-1 signaling, with pDCs that did not produce IFN-1 in response to SARS-CoV-2 (Zhang et al., 2020). An accompanying study found that 10% of patients with critical COVID-19 infection had circulating neutralizing autoantibodies against IFN-1. These autoantibodies were pre-existing and were a cause of severe disease rather than a consequence of infection. Remarkably, 94% of these patients were men, half of whom were aged >65 years, and more than a third died from COVID-19 (Bastard et al., 2020).

EXCEPTIONAL INNATE IMMUNITY MAY PROVIDE RESISTANCE TO VIRAL INFECTION WITHOUT ENGAGING THE ADAPTIVE IMMUNE SYSTEM

In theory, robust innate and intrinsic immune responses may be sufficient to clear a viral exposure without triggering antibody production. This is a difficult phenomenon to study because most patients with viral clearance are identified by their postinfectious seroconversion. However, potential resistance to hepatitis C virus (HCV) infection has been described in high-risk injection drug users who lack HCV-specific T-cell responses and seroconversion despite a long history of HCV exposure, suggesting that individuals may be resistant to viral infection or protected from viral replication by an exceptional innate antiviral response without seroconversion (Shawa et al., 2017). The pandemic provides an opportunity to investigate antiviral resistance through the study of close contacts of patients with critical COVID-19 who remain asymptomatic and seronegative. Patients with pandemic-associated pernio may also serve as a model for a mild or resistant SARS-CoV-2 phenotype and are readily identifiable by their skin findings.

ASSOCIATION OF PERNIO/CHILBLAINS WITH MONOGENIC DISORDERS OF CONSTITUTIVELY ACTIVE IFN-1 PRODUCTION

Both clinically and histologically, pandemic-associated pernio mimics the skin lesions of familial chilblain lupus and Aicardi–Goutières syndrome, which are characterized by IFN-1 excess. These monogenic disorders, referred to as type 1 interferonopathies, are caused by mutations associated with impaired nucleic acid sensing that lead to sustained and upregulated IFN-1 signaling (Rice et al., 2007; Uggenti et al., 2019; Zimmermann et al., 2019). In affected patients, pernio develops in early infancy, followed by systemic vasculopathy due to autoinflammation. IFN-1 is profoundly increased in affected skin and blood. Similar to pandemic-associated pernio, cold is a critical precipitant. In familial chilblain lupus, 5-day cold exposure of primary fibroblasts followed by rewarming enhanced ROS, a known trigger of DNA damage, and increased IFN-1 activation, switching cells from a quiescent to a proinflammatory state (Günther et al., 2015).

INVESTIGATION OF COVID TOES IDENTIFIES SPIKE PROTEIN

COVID-19 autopsy studies have shown a SARS-CoV-2 tropism for the skin. Angiotensin-converting enzyme 2 (ACE2), the SARS-CoV-2 receptor, is expressed on dermal blood vessels, the basal layer of the epidermis, and unexpectedly on eccrine glands (Hamming et al., 2004) (Figure 1b). We hypothesize that this expression may explain the localization of inflammation to hands and feet because these sites harbor the highest concentration of eccrine glands.

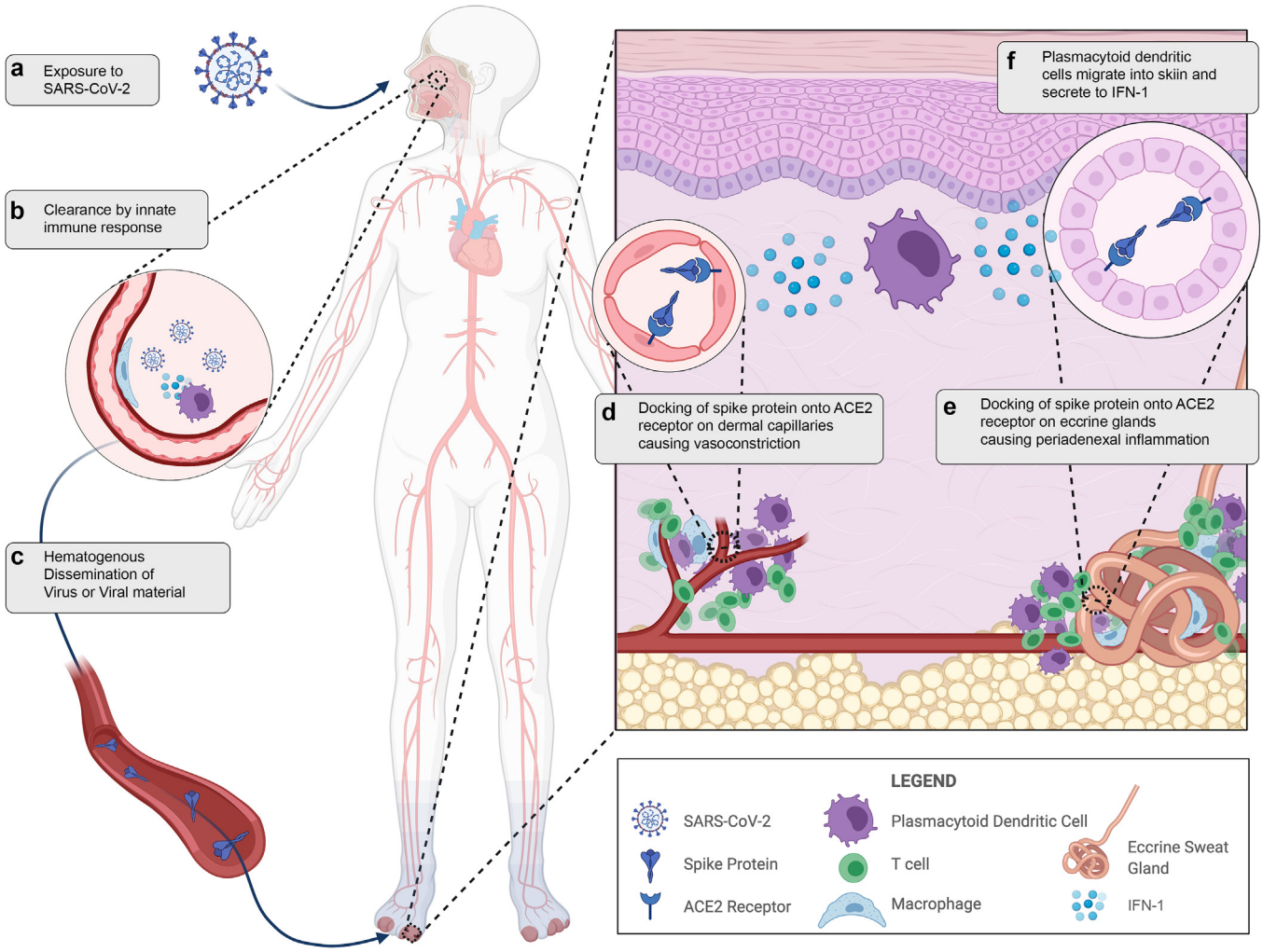

Figure 2. Illustrated hypothesis of pandemic-associated pernio pathophysiology. (**a**) Viral exposure to SARS-CoV-2 in the environment. (**b**) SARS-CoV-2 is cleared by a robust innate immune response in the nasopharynx. (**c**) There is hematogenous showering and dissemination of viral material or virus. (**d**) Docking of spike protein to the ACE2 receptor on dermal capillaries results in vasoconstriction and perivascular inflammation. (**e**) Docking of spike protein to ACE2 receptors on eccrine glands results in periadnexal inflammation. (**f**) Plasmacytoid dendritic cells, the major contributor to IFN-1 response, migrate to the skin in response to viral material. ACE2, angiotensin-converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

This is further supported by the recent demonstration of SARS-CoV-2–associated spike protein in cutaneous vascular endothelium and eccrine glands in biopsies from patients with COVID toes (Colmenero et al., 2020; Ko et al., 2021; Magro et al., 2021; Moon et al., 2021; Santonja et al., 2020). It should be noted that not all biopsy specimens detected spike protein, which could reflect the timing and depth of skin biopsy. Importantly, nucleocapsid antibody staining has been negative.

The immunohistochemistry patterns in published studies, coupled with lack of detection of viral RNA by in situ hybridization or PCR from tissue, suggests that pandemic-associated pernio may result from hematogenous spread of viral material and may not require viral replication in the skin (Herman et al., 2020; Ko et al., 2021). Emerging reports of pernio after mRNA vaccination also raise speculation that this could be an immune response to viral proteins or RNA without viral replication (Davido et al., 2021; McMahon et al., 2021). In unaffected skin of patients with critical COVID-19 infection, Magro et al. (2020) found microvascular complement deposition (an end-terminal event driving thrombosis) strongly colocalized with spike protein and the ACE2 receptor but without in situ evidence of viral RNA. The colocalization of the ACE2 receptor and viral capsid proteins suggests that circulating viral debris may dock onto the endothelium/eccrine ducts. This would be consistent with the hypothesis that patients with pandemic-associated pernio clear the SARS-CoV-2 through a robust IFN-1 response but shower viral debris that binds ACE2 receptors in the skin. Finally, the renin-angiotensin system (RAS) is expressed locally in the skin and may be indirectly activated by ACE2 binding from SARS-CoV-2 (Moon et al., 2021; Silva et al., 2020; Steckelings et al., 2004). We hypothesize that persistent vasoconstriction, poor capillary refill, and the chronicity of the response in some patients could also be linked to local cutaneous RAS activation (Figure 2).

EVIDENCE OF ROBUST IFN-1 RESPONSE IN COVID TOES

Pandemic-associated pernio exhibits a lymphocytic infiltrate in a perivascular and perieccrine distribution (Figure 1b),

which is composed predominantly of lymphocytes and pDCs. pDCs are responsible for the initiation of IFN-1 signaling in response to recognition of viral RNA. Immunohistochemistry studies have revealed robust MxA staining (a downstream product of IFN-1 activation) in affected specimens in a perivascular and perieccrine distribution (Aschoff et al., 2020). A recent paper suggested a viral-induced interferonopathy in affected patients, demonstrating a significant increase of in vitro IFN-α production after stimulation compared with that in patients with mild or severe acute COVID-19 infection (Hubiche et al., 2021).

COLD FEET: AMBIENT TEMPERATURE AFFECTS VIRUS–HOST RESPONSES

A cold environment is crucial to the induction of COVID toes. Humans maintain a narrow range of core body temperatures through neural, vascular, and biochemical mechanisms. Increases in body temperature through fever enhance immune function and pathogen killing. Colder ambient temperatures are known to diminish the efficiency of the innate immune response, facilitating viral replication in other infections (Foxman et al., 2015). Indeed, in vitro SARS-CoV-2 replication significantly increases with colder temperatures, demonstrating 10-fold higher infectious titers when incubated at 33 °C versus incubating at 37 °C (V'kovski et al., 2021). Importantly, attenuated IFN-1 expression is responsible for the increased viral replication efficiency at 33 °C. In pandemic-associated pernio, one could hypothesize that after clearance from the warmer respiratory tract, dispersed viral material settles at these colder acral sites owing to skin tropism through ACE2 expression, evading immune clearance. With rewarming of the toes, a local IFN-1 response could be initiated by pDCs after migration into the skin.

CONCLUSIONS

The striking spatial and temporal association with the pandemic, the accumulating evidence of both viral material and MxA in the affected skin, and the biologic plausibility of pernio linked to the critical role of IFN-1 signaling in COVID-19 all suggest a causal linkage with SARS-CoV-2. This evidence implicates a robust IFN-1 response in affected patients. The absence of antibody production supports rather than undermines this hypothesis because an exceptional innate and intrinsic immune activity may be enough to clear the viral infection without seroconversion. These findings further intimate IFN-I signaling in host outcomes to COVID-19.

In cooperation with the National Institutes of Health–funded Human Genome Effort and the International COVID Human Genomic Effort, the COVID toes biobank at the University of Wisconsin-Madison seeks to identify the genetic and immunologic basis to provide clinically relevant insights into SARS-CoV-2–associated pernio and could provide a framework for considering preventative approaches to SARS-CoV-2 infection utilizing early administration of IFNs.

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CONFLICT OF INTEREST

The Authors have no conflict of interest.

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