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When interferon tiptoes through COVID-19: Pernio-like lesions and their prognostic implications during SARS-CoV-2 infection

To the Editor: It was recently reported that patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can develop cutaneous lesions resembling pernio (popularly called "COVID toes").[1-5] Recent work has suggested that SARS-CoV-2 infection is sometimes characterized by a muted antiviral type I and III interferon (IFN) response,[6,7] which may explain progression to severe clinical manifestations in some patients; whereas a robust type I IFN response was associated with rapid viral clearance and bland disease course.[6] Here, we describe pernio-like lesions as they have been reported in the literature and consider other settings where pernio is observed, including familial chilblains lupus (FCL), an interferonopathy syndrome. Together, these data suggest that COVID toes may be a marker of patients who are able to mount a robust antiviral immune response to SARS-CoV-2 and reflect a milder course of coronavirus disease 2019 (COVID-19).

Sporadic pernio (also known as chilblains) is an idiopathic cold-sensitive inflammatory disorder that presents with red-to-violaceous macules or papules on acral sites; vesiculation and ulceration may occur. These lesions are typically located on the distal toes but can also occur on fingers, heels, and even the nose and ears. Histopathology reveals edema in the superficial dermis and marked superficial and deep perivascular and perieccrine lymphocytic inflammation (Fig 1, *A*). Interface change or vasculopathic changes (eg, focal thrombosis), or both, may be present.

Similar cold-induced lesions are a feature of FCL, caused by mutations in *TREX1*. TREX1-FCL is one of several interferonopathies, genetic syndromes characterized by excessive, type I IFN production.[8] Type I IFNs (IFN-α, IFN-β) are essential inducers of antiviral immunity but also can drive autoimmunity when activated inappropriately. The clinical and histologic manifestations of pernio in TREX1-FCL are similar to sporadic pernio but can be more severe. Therefore, pernio can be a manifestation of a systemically elevated type I IFN response. Furthermore, others have shown that recombinant type I IFN therapy can induce thrombotic microangiopathy in some patients through direct effects on the microvasculature.[9]

Pernio-like lesions in the setting of SARS-CoV-2 infection have primarily been described in relatively younger patients who tend to have a milder disease course.[1-5] Similar to idiopathic pernio and TREX1-FCL, histopathology reveals superficial and deep perivascular and perieccrine lymphocytic inflammation and mild vacuolar interface change with

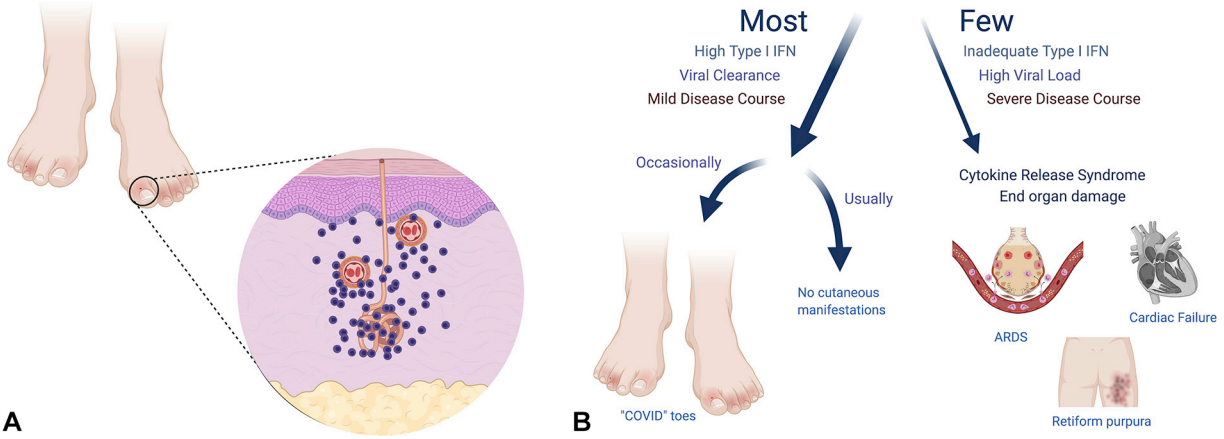

Fig 1. Clinical presentation of pernio-like lesions, histology, and disease course, depending on type I interferon response. **A,** Histology of pernio and pernio-like lesions. There is a moderately dense superficial and deep perivascular lymphocytic or lymphohistiocytic inflammatory infiltrate. There is also perieccrine lymphocytic inflammation. A mild vacuolar interface dermatitis can also be seen. **B,** Interferon (*IFN*) and clinical manifestations of coronavirus disease 2019 (COVID-19). A strong, early type I IFN response is associated with viral clearance and a mild course, whereas an insufficient type I IFN response may lead to severe disease, possibly through development of a cytokine release syndrome and subsequent end-organ damage. Pernio-like lesions, or COVID toes, which we know can result from elevated type I IFN signaling in the body, may be a marker of those who respond effectively to the virus.

occasional microthrombi.[2,3] Lesions often resolve over days to weeks.

Interpretation of this particular manifestation of COVID-19 has been somewhat hampered by low rates of SARS-CoV-2 confirmation in reported cases, but the apparent relationship of pernio-like lesions and a mild disease course may be explained by a high type I IFN response in such patients. Recent observations suggest that a strong early type I IFN response is associated with early viral control and a mild course, whereas an insufficient type I IFN response may be associated with progression to more severe disease (Fig 1, *B*).[6,7] Therefore, we hypothesize that pernio-like lesions, which can occur with elevated type I IFN signaling, are the result of a robust antiviral response in patients with COVID-19 and, therefore, are associated with a favorable disease course, as observed in these patients.

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