

# Post-vaccination COVID Toes (Chilblains) Exacerbated by Rituximab Infusion Suggests Interferon Activation as Mechanism

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**ABSTRACT** Coronavirus disease (COVID) toes are pernio-like skin lesions associated with severe acute respiratory syndrome coronavirus 2. We observed pernio-like skin findings presenting after a Pfizer BioNTech vaccine, which significantly worsened after an infusion of rituximab. This suggests that the mechanism for COVID toes is interferon activation. Military providers may avoid unnecessary referrals for this self-limiting condition by anticipating this adverse effect.

## INTRODUCTION

Novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections continue to present a vexing constellation of symptoms, including skin findings. Several theories have been proposed to explain the pathophysiology of coronavirus disease 2019 (COVID-19)-related signs and symptoms, most involving antibody- and immune-mediated responses against endothelial and vascular tissues, causing a constellation of vascular phenomena depending on the organ system affected.<sup>1</sup> The COVID-19-associated pernio, or COVID toes, appears to be a rare but known symptom of COVID-19 infection, particularly in pediatric patients. The incidence is unclear due to the sparse number of cases.<sup>2</sup>

The mechanism of COVID toes remains uncertain. Hypotheses include processes similar to those that cause sporadic pernio, known as chilblains, and pathways centered on inflammatory mechanisms that may induce microangiopathic coagulopathy or vasculitis. Several idiopathic, congenital, and autoimmune cutaneous presentations similar to that of COVID toes share mechanistic immune responses, among which include elevated type I interferon (IFN) signaling.<sup>3,4</sup> While the role of autoimmune disease in COVID toes development has not been well defined, the type I IFN pathway has been connected to several rheumatic diseases<sup>3,5</sup> and subsequent therapeutic response in immunomodulatory interventions such as rituximab.<sup>5,6</sup>

The U.S. Food and Drug Administration has granted Emergency Use Authorization to three COVID-19 vaccines, one each from Pfizer BioNTech, Moderna, and Johnson &

Johnson Janssen.<sup>7</sup> As of March 2021, 359 million vaccines have been administered worldwide, with over 107 million administered in the USA.<sup>8</sup> Adverse effect data for the Pfizer BioNTech vaccine reported in January 2021, via the Centers for Disease Control's V-safe after vaccination health checker tracking system, showed that after one dose, common adverse effects were pain (68%); fatigue (29%); headache (26%); myalgias (17%); chills, fever, joint pain, nausea, and swelling (7%).<sup>9</sup> Serious adverse effects were noted to be 48 per 1 million doses administered, with only 50 cases of anaphylaxis reported by the end of January 2021 with the Pfizer BioNTech vaccine.<sup>9</sup> No reports of COVID-19-related pernio-like lesions have been reported through Vaccine Adverse Event Reporting System (Department of Health and Human Services) following the administration of any COVID-19 vaccination to date, although there is a single report from France that documents similar findings.<sup>10</sup>

## CASE HISTORY

A 46-year-old woman, known to be SARS-CoV-2 naïve, but with a medical history significant for seronegative rheumatoid arthritis, Sjögren's syndrome, and type 2 diabetes mellitus, presented to an outpatient clinic with worsening soreness and pernio-like lesions on the toes of both feet. She reported symptoms of mild soreness, swelling, and discoloration in the toes of both feet appearing approximately 2 weeks after her first Pfizer BioNTech COVID-19 vaccine mid-December 2020. These symptoms worsened within hours of receiving her second dose in mid-January 2021 (Fig. 1). One week after noticing these worsening symptoms, she was evaluated by her rheumatologist and referred to dermatology (Fig. 2). The dermatologist noted pernio-like lesions and prescribed 0.05% clobetasol cream to be applied as needed twice a day for 14 days with at least a 5-day hiatus between further applications. The patient applied this cream twice daily and noticed improvement without complete resolution over the following 10 days. On day 10 of treatment, she received a routine scheduled infusion of 1 g of rituximab. Within hours of this infusion she noticed marked worsening of her skin symptoms on her feet (Fig. 1). The following day she presented to primary care

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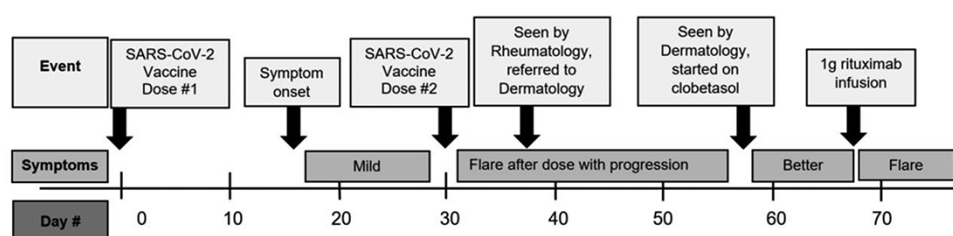
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**FIGURE 1.** Patient's right foot after her second coronavirus disease 2019 (COVID-19) vaccine (left). Patient's feet after her rituximab infusion (right).



**FIGURE 2.** Timeline of events.

for further evaluation (38 days after her second vaccine dose and 1 day post rituximab infusion).

At her primary care visit, the patient reported that the lesions had already improved overnight. On examination, her feet showed violaceous, edematous distal phalanges to bilateral midfoot, and open lesions on the distal tip of the right second and left fourth digit productive of scant, clear, serosanguinous fluid. The patient was afebrile, in no distress, with no increased warmth overlying the areas of discoloration, no streaking, and no loss of distal sensation. The affected areas were pain free but tender to palpation. The patient gave written consent for use of her records and images. She was advised to continue the clobetasol regimen with the planned 5-day hiatus and follow up if symptoms continued to get worse.

## DISCUSSION

Coronavirus infections are particularly harmful to humans due to suppression of the type I IFN response, which is critical for protection against viral infections.<sup>4</sup> A high type I IFN response to SARS-CoV-2 infection is associated with lower severity of disease and is hypothesized as a cause of pernio-like lesions, commonly referred to as COVID toes.<sup>1,11</sup> Pernio-like lesions are not listed as an adverse effect to the Pfizer BioNTech COVID-19 vaccine,<sup>12</sup> and to our knowledge have not been reported in the U.S. literature as an adverse effect of any COVID-19 vaccine.

We believe this is the second documented case of pernio-like lesions following the administration of the COVID-19

vaccine.<sup>10</sup> As the patient was not infected with SARS-CoV-2, this suggests that the mechanism of COVID toes is not a direct effect of SARS-CoV-2 infection, but rather the result of the host's immune response to such an infection. Further, in a patient with a history of several years of treatment with rituximab without any cutaneous adverse effects, the marked worsening of COVID toe lesions following rituximab administration only in the context of COVID-19 vaccination supports the mechanism of type I IFN activation as the etiology, as rituximab can activate the type I IFN system in patients with low baseline IFN-response activity.<sup>6</sup>

## CONCLUSIONS

This case suggests type I IFN activation is the likely mechanism of the development of COVID toes and warrants prospective study to confirm or refute this hypothesis. Regardless of mechanism, this finding of COVID toes following COVID-19 vaccination is an important finding for primary care physicians to be aware of. If this mechanism is confirmed, other clinical sequelae may also be anticipated. Increased type I IFN activity may exacerbate psoriasis and systemic lupus erythematosus symptoms, but may improve symptoms of multiple sclerosis and serve as an adjuvant therapy for several cancers.<sup>3</sup>

As universal vaccination is pursued in civilian and Department of Defense personnel,<sup>13</sup> we can expect to see many more patients exhibiting this benign, self-limited condition. This is particularly relevant for military primary care providers who

may not have proximal access to dermatology support and for any provider caring for patients receiving immunomodulatory medication. Patient education before COVID-19 vaccination in these populations regarding the possible development of COVID toes may prevent unnecessary referral and excessive healthcare utilization.

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## CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

## DATA AVAILABILITY

The data used for this case are available from the corresponding author on reasonable request.

## ETHICAL APPROVAL

This research was approved by the Mayo Clinic Institutional Review Board.

## AUTHORS' CONTRIBUTIONS

J.W.Q.: analysis of data, interpretation, and substantial revision. Y.D.: acquisition, analysis, interpretation, and drafting the work. M.E.W.: analysis of data, interpretation, and substantial revision. C.M.Z.: analysis of data, interpretation, and substantial revision. T.J.D.: analysis of data, interpretation, and substantial revision. R.P.L.: acquisition, analysis, interpretation, and substantial revision. All authors read and approved the final manuscript.

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