

“COVID Toes” in Three Siblings

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Abstract: Dermatologists reported an outbreak of pernio (red to purple swollen painful toes) during the COVID-19 pandemic. Most subjects lacked positive CoV-19 polymerase chain reaction (PCR) or antibodies or a preceding illness. The dermatologists termed the illness “COVID toes.” Pernio usually affects adults versus “COVID toes” usually children. Pernio is preceded by a clear history of exposure to wet and cold. Patients with “COVID toes” lack this history. Also, it is not unusual for multiple family members to have “COVID toes.” Our case report describes “COVID toes” in an 18-year-old with no preceding illness, a negative SARS-CoV-19 PCR, and an initially negative SARS-CoV-19 antibody, and also his 2 siblings also developed “COVID toes.” In our index case, repeat SARS-CoV-19 antibodies were positive. Seroconversion has rarely been reported in patients with “COVID toes.” Why most “COVID toes” patients lack a clinical history of COVID-19 and are SARS-CoV-19 PCR and antibody negative is a mystery.

Key Words: COVID toes, COVID-19, pernio

Pernio (from the Latin, haunch of the leg) or chilblains (from the Anglo-Saxon, “chil” meaning cold and “blains” meaning sores) is a dermatologic condition characterized by edema, erythema and red/purple macules, papules, plaques and/or nodules of the acral surfaces including toes and fingers. The affected digits may itchy, burning and painful. Pernio is caused by exposure to damp and cold. Most cases of pernio occur in adults and lesions appear within hours of cold exposure. Associated with the COVID-19 pandemic, there has been an outbreak of chilblains-like lesions reported by dermatologists. These patients with chilblains-like lesions differ from pernio in that (1) chilblains-like lesions affect children more than adults; (2) patients with chilblains-like lesions lack a history of exposure to cold; and (3) multiple family members with chilblains-like lesions may be affected, which is not a characteristic of pernio. These chilblains-like lesions usually involve the toes and have been named by dermatologists “COVID toes.”^{1,2}

CASE PRESENTATION

A 10-year-old male developed red toes on November 27, 2020. He had been well with no preceding illnesses and no cold or wet exposure. Over the next week, his toes became swollen with a blue/purple discoloration distally and erythema proximally (Fig. 1). His toes had many painful red to violaceous papules and nodules. On December 2, 2020, he was tested by nasopharyngeal swab for SARS-CoV-19 by polymerase chain reaction (PCR) and was negative. Over the next 2 weeks, his toes became so tender that he could not wear socks. He developed some painful purple nodules on his heels and sides of his feet. He had no systemic signs or symptoms

other than his painful toes and feet. His toes were so painful that he had trouble sleeping because of the sheets touching his toes. On December 16, 2020, he had a SARS-CoV-2 antibody performed that was negative. In addition, he had a normal complete blood count with a white blood cell of 4400/mm³ (29% lymphocytes and 54% neutrophils). He had a negative antinuclear antibodies, and a normal C-reactive protein and erythrocyte sedimentation rate. His ferritin and d-dimer were normal. Epstein-Barr virus antibodies were negative. Parvovirus antibodies and parvovirus PCR were also negative. He was then treated with indomethacin and nifedipine, which somewhat relieved his pain.³ A repeat SARS-CoV-2 antibody (1/4/21) was positive (SARS-CoV-2, IgG, www.QuestDiagnostics.com/Covid19). Six weeks after onset of the red toes, the pain resolved and his toes peeled (Fig. 2).

The patient lived with his mother, his 15-year-old brother and his 12-year-old sister. They all had been well, and there was no history of illness. On December 6, 2020, our patient’s brother developed red painful toes (Fig. 3) that over the 7 days became red, blue and very painful. Our patient’s 12-year-old sister also developed red, itchy toes on December 6, 2020 (Fig. 4). The sister had mild involvement, with only 3 toes involved of each foot. On December 8, 2020, the 15-year-old and 12-year-old were tested with a nasopharyngeal swab for COVID-19 by PCR and were negative. A month later (January 4, 2021), they were both tested for COVID-19 antibodies and were negative. The children’s mother was also tested (January 4, 2021) for COVID-19 antibodies and was negative. For our index patient, SARS-CoV-19 antibodies were initially negative (20 days after onset of toe symptoms) but positive 39 days after onset. His 2 siblings were again tested for COVID-19 antibodies (2/1/21), and again were negative.

DISCUSSION

In March 2020, weeks after the onset of COVID-19 in Italy, Mazzotta et al⁴ reported an outbreak of chilblains-like toe lesions in healthy children with no exposure of their feet to wet and cold, and negative histories for COVID-19. Ten per cent of the cases occurred in siblings. In some cases, the children had been exposed to family members with COVID-19. Piccolo et al⁵ reported a case series of 63 subjects with chilblains-like lesions occurring during the Italian COVID-19 pandemic. Feet alone were affected in 86% of cases. Most subjects complained of pain and/or itch; 25% had skin lesions without symptoms. Respiratory symptoms preceded the chilblains-like lesions in only 8% of subjects. Two subjects had siblings with similar findings. Eleven patients had SARS-CoV-19 PCR tests performed and 2 of 11 (18%) were positive; SARS-CoV-19 antibodies were performed for 6 subjects and 2 of 6 (33%) were positive. Massey and Jones³ reviewed 566 patients with chilblains-like lesions that occurred during the COVID-19 pandemic and the majority were both SARS-CoV-19 PCR and antibody negative. Dermatologists from around the world recognized the increase of chilblains, and the colloquialization “COVID toes” was coined. Most cases of “COVID toes” were reported in pediatric patients and, if tested, only 15% of “COVID toe” patients had a positive SARS-CoV-19 PCR and/or antibody.³ To better understand “COVID toes” a dermatology “COVID toe” case registry has been set up—The Pediatric Dermatology research Alliance COVID-19 Response Task Force.

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H.M.F. cared for these patients and wrote the case report and discussion. H.M.F. has approved the final manuscript as submitted and he agrees to be accountable for all aspects of the work.

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FIGURE 1. A 18-year-old with painful swollen toes with a blue discoloration distally and erythema proximally.

The pathogenesis of “COVID toes” has yet to be defined. A skin biopsy of pernio versus “COVID toes” may appear identical. Both show edema and perivascular lymphocytic infiltrates.⁶ Patients hospitalized with severe COVID-19 can develop ischemic lesions of the extremities due to thrombosis, associated with hypercoagulation. This is associated with antiphospholipid antibodies. In these cases, there is wide-spread skin involvement due to thrombosis. This is clearly different from “COVID toes,” which usually appear as a single entity in an otherwise well patient.

Since pernio and “COVID toes” may be the same histologically, it has been theorized that family members in quarantine, because of COVID-19, may be at home and barefoot. In this setting it is more likely to get pernio.⁷ However, this explanation is unlikely, as exposure to wet and cold has not been reported among patients with “COVID toes.” Another possibility is that “COVID toes” result from direct endothelial damage by SARS-CoV-19. Colmenero et al⁸ reported finding SARS-CoV-19 by histochemical staining in epithelial and endothelial cells in biopsy specimens. These findings, however, may be nonspecific have not been confirmed. Another hypothesis is that young subjects mount a super type 1 interferon (IFN-1) response on exposure to SARS-CoV-19. This response stops viral replication (thus, negative SARS-CoV-19 PCR and antibodies), but the resultant cytokine storm induces the microangiopathic changes of “COVID toes.”⁹



FIGURE 2. Peeling toes of the 18-year-old, after 6 weeks of swelling, pain and purple discoloration.



FIGURE 3. Red painful toes in the index patient's 15-year-old brother.

There are multiple aspects of “COVID toes” that are difficult to explain and, thus, a controversy as to the causation of “COVID toes” by SARS-CoV-19 versus an epiphenomenon. The dramatic increase of pernio during the COVID-19 pandemic was first recognized by dermatologists. An academic dermatologic department in Minnesota reported 9–10 new diagnosis of pernio per year before the pandemic. These numbers increased >5-fold after the onset of the pandemic.¹⁰ These increases in pernio have been reported worldwide. First, most patients with “COVID toes” give a negative history for a preceding documented or undocumented COVID-19 infection or exposure. Second, testing for SARS-CoV-19 PCR and antibodies are also frequently negative. Massey and Jones³ reviewed 13 reports and 41 of 172 (24%) of “COVID toe” patients tested positive by PCR or serology. (In the largest of these 13 studies, 29 of 71 (41%) tested positive versus the other 12 study results 11 of 101 (11%) positive. Thus, in an outlier study, Caseli et al¹¹ tested 38 “COVID toe” patients by PCR and/or serology and 0 of 38 (0%) tested positive. Hubiche et al¹² in a study of 40 patients with “chilblain-like lesions” reported that 0 of 40 had positive SARS-CoV-19 PCRs and 12 of 40 had positive SARS-CoV-19 antibodies. Methods used for testing varied among the studies, which may



FIGURE 4. Red nonpainful toes (left foot second, third and fifth toes, and right foot second, third and fourth toes) in the index patient's 12-year-old sister.

explain inconsistencies. Some argue that the patients with “COVID toes” who test positive for COVID-19 are random.⁷ Seroconversion would be more convincing.

McMahan et al¹⁰ described a patient with “COVID toes” who tested negative for SARS-CoV-19 by PCR and antibody 2 weeks after onset, but repeat serology 21 days later was positive. Our index case also showed seroconversion during his “COVID toes” illness, thus, making SARS-CoV-19 the likely culprit.

Most cases of “COVID toes” are mild and need no treatment. There are no studies addressing the treatment of moderate to severe cases of “COVID toes”; however, nonsteroid anti-inflammatory agents have been used empirically. Traditional treatments of pernio can be tried for the treatment of “COVID toes.” These include oral antihistamines for itch, oral nonsteroid agents for pain and inflammation, topical steroids for inflammation and calcium channel blockers for inflammation. Because our index case had severe pain, we tried indomethacin and a calcium channel blocker. Calcium channel blockers have been studied for the treatment of pernio with mixed results.^{3,13}

Clinically and pathologically, pernio and “COVID toes” are indistinguishable. However, patients with pernio give a clear history of an exposure to wet and cold within hours of developing toe symptoms versus subjects with “COVID toes” rarely give such a history. The mystery of “COVID toes” is patients rarely have a preceding history of COVID-19 or a COVID-19 like illness. In addition, they are negative for SARS-CoV-19 by PCR and antibody testing. Most likely, there is a COVID-19 marker that awaits discovery.

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