CASE STUDY

Histopathology of persistent long COVID toe: A case report

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Abstract

During the 2020 coronavirus (SARS-CoV-2) pandemic, several cutaneous lesions were identified, including pseudo-chilblain, vesicular, urticarial, maculopapular, and livedo/necrosis. A 59-year-old obese man with probable COVID-19 developed painful cyanosis with histopathologic capillary thrombosis of toes, and the cyanosis persisted for nearly 22 months. Shortly after initial exposure to family members with documented SARS-CoV-2, he developed upper respiratory symptoms, yet his anti-SARS-CoV-2 antibody and nasal swab RT-PCR tests were repeatedly negative. Two family members were hospitalized and one of them succumbed with documented SARS-CoV-2 pneumonia within 10 days of exposure. Biopsy specimen of the distal toe 16 weeks after initial exposure showed papillary dermal capillary thrombosis with endothelial swelling, telangiectasia, and peri-eccrine lymphocytic infiltrates resembling pernio. Overall, this is the first case of biopsy specimen of “long COVID toe” following presumed SARS-CoV-2 exposure, with a demonstration of thrombotic vasculopathy, toe cyanosis, and pernio-like pathology.

KEYWORDS
capillary occlusion, COVID toe, COVID-19, fibrin thrombi, pernio, SARS-CoV-2

INTRODUCTION

Chilblain-like acral lesions account for nearly one in five cutaneous COVID-19 presentations.¹ These chilblain-like or pseudo-chilblain lesions around the distal extremities have been termed COVID purpura, or “COVID toe” and may present in the absence of respiratory and gastrointestinal symptoms.²,³ Skin lesions associated with COVID-19 have been documented in pediatric, adult, and geriatric populations.⁴ We describe biopsy findings of a patient who presented with “COVID toe” 16 weeks post-exposure, with both pernio-like lymphocyte infiltrate and capillary occlusion by fibrin thrombi (Figure 2B–F).

CASE REPORT

A 59-year-old obese white male presented to his podiatrist clinic with painful, swollen cyanotic toes of the left foot (Figure 1A–I). This patient reported that 10 weeks earlier, he had been in close contact with two individuals at a family dinner who were diagnosed with COVID-19 2 days later, and one of whom succumbed to the illness. Following exposure, our patient reported fever and upper respiratory symptoms that resolved within a week. Persistent burning acral pain developed shortly thereafter.

Physical examination showed toe cyanosis and edema. The toes were tender to palpation with normal capillary refill and normal pedal pulses. The temperature, sensation, range of motion, and muscle strength of the toes were also found to be normal. Radiographs were negative. Past medical history included hypertension; current medications included a daily 50-mg oral dose of losartan potassium (angiotensin receptor antagonist), a daily 81-mg oral acetylsalicylic acid, and multivitamins.

Initially, the patient was prescribed celecoxib, a non-steroidal anti-inflammatory drug, and advised to keep his toes warm and avoid exposure to cold water or cold temperatures. However, his toes failed to improve and upon return, the third toe appeared more cyanotic.
**Figure 1** Distal rugosity and cyanosis with proximal erythema persisting for nearly 22 months post-COVID-19 exposure. (A, B) May 26, 2020 (12 weeks post-exposure); (C, D) September 18, 2020 (28 weeks post-exposure); (E, F) December 2, 2020 (39 weeks post-exposure); (G, H) January 4, 2021 (44 weeks post-exposure); (I) May 4, 2021 (first dose: March 23, 2021, second dose: April 29, 2021; 61 weeks post-exposure)

**Figure 2** Long COVID toe histopathology. (A) Low-power photomicrograph (H&E, ×26). (B) Fibrin thrombi occluding capillaries in dermal papillae (H&E, ×130). (C) Fibrin thrombi occluding capillaries in dermal papillae (anti-fibrin antibody; confocal fluorescence microscopy, ×200). (D) Fibrin thrombi occluding capillaries in dermal papillae (H&E, ×400). (E) Pernio-like lymphocytic infiltrate in eccrine glands (H&E, ×110). (F) Green fibrin thrombi occluding capillaries in dermal papillae with blue DAPI+ nuclei (fluorescein labeled anti-fibrin antibody; confocal fluorescence microscopy, ×630)
than the others, and a 3-mm punch biopsy specimen was obtained 16 weeks post-exposure. SARS-CoV-2 PCR was repeatedly negative. Anti-SARS-CoV-2 antibody, Epstein–Barr virus PCR, parovirus B19, C-reactive protein, ferritin, sedimentation rate, d-dimer, and prothrombin time were also negative.

Histopathologically, fibrin thrombi occluded many papillary dermal capillaries having endothelial cell swelling and pauci-cellular inflammatory cell response, mainly deep dermal infiltrate of small lymphocytes in and around eccrine coils (Figure 2E). Fibrin thrombi stained weakly PAS+ and stained intensely with rabbit polyclonal anti-fibrin antibody by direct immunofluorescence technique (Figure 2F; cat. no. RB-1924-R2; NeoMarkers; batch #1924R2004A) using epiluminescence microscopy (Olympus BX61 Olympus USA) and confocal fluorescence microscopy (Leica SP8X). Immunohistochemistry for 1A9 monoclonal antibody against SARS-CoV/SARS-CoV-2 (COVID-19) spike protein (dilution 1:200, cat. no. GTX632604; GeneTex, Inc.; batch 43 937) was negative, except for focal weak staining of single epidermal basal keratinocytes and no endothelial staining was observed (not shown). A human lung biopsy specimen with confirmed COVID-19 positivity was used as positive stain control. The immunostain to spike protein was interpreted as negative because of the low-intensity staining of a few keratinocytes in the basal layer. The pain diminished with 2% nitroglycerin applied to each toe daily. However, the toes became cyanotic and erythematous and remained so for nearly 22 months, worsening after the second dose of COVID-19 vaccine (Pfizer-BioNTech BNT162b2; Figure 1).
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