

“Blue toes” following vaccination with the BNT162b2 mRNA COVID-19 vaccine

Benjamin Davido (MD, MSc)¹, Helene Mascitti (MD, MSc)¹, Marc Fortier-Beaulieu (MD)¹,
Karim Jaffal (MD)¹, Pierre de Truchis (MD, MSc)¹

1. Maladies Infectieuses, Hôpital Universitaire Raymond-Poincaré, AP-HP, Garches

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I confirm that all listed authors have contributed to this work and approved the paper.

Corresponding author:

B. Davido, MD, MSc

Infectious Diseases Department

Raymond Poincaré Teaching Hospital

Garches 92380, France

Tel : +33-1- 47107758

Email: benjamin.davido@aphp.fr

Highlights : COVID toes can be encountered in young individuals during acute COVID-19 infection while it results from the direct action of Spike protein on vessels. We report the case of COVID toes during the French campaign of vaccination that occurred 4 days after the vaccination with the Pfizer-BioNTech mRNA vaccine against COVID-19.

A young Caucasian female aged of 41 years-old, non-smoker, with a medical history of bipolar disorder under valproate for more than 10 years, consulted for the evaluation of

chilblain-like skin changes on her toes. She reported no previous signs compatible with Raynaud's syndrome. She presented a sudden toe pain with walking impairment and itching at night, that appeared 4 days after the first injection with the Pfizer-BioNTech-162b2 vaccine against COVID-19. She was otherwise asymptomatic, especially with no ear-nose-throat symptoms or fever and nasopharyngeal SARS-CoV-2 PCR was tested twice negative. Physical examination performed 10 days after the vaccination revealed non-tender violaceous toes of the left foot (Figure) without any other dermatological lesion, especially no exanthema while cardiovascular and pulmonary examinations were strictly normal.

Standard biological tests performed at the beginning of symptoms revealed no abnormalities. White blood cells and lipid profile were strictly normal, serum creatinine and CRP value were 70 mmol/L and <1 mg/L, respectively, with a normal doppler ultrasonography of the lower limb arteries arguing against a cholesterol embolization syndrome. Further investigations confirmed no argument for a systemic vasculitis: absence of significant antinuclear antibodies (titer of 1:160 without anti-DNA or anti-ENA), ANCA, cryoglobulin, cold agglutinin or antiphospholipid syndrome. A cardiac echography ruled out an infective endocarditis, and a nailfold capillaroscopy was performed to ensure she had no systemic sclerosis.

Therefore, a clinical diagnosis of COVID toes-like syndrome was suggested, considering all the various dermatological lesions encountered during acute COVID-19 infection.¹ Indeed, COVID toes became a hallmark of the disease in young and largely asymptomatic outpatients, commonly with a negative test result for SARS-CoV-2 infection.² Furthermore, ECLIA Cobas Roche © anti-Nucleocapsid (N) antibodies remained negative meanwhile she began to have some anti-Spike (S) antibodies at a low-level (0.642 UI/mL) 12 days after the first injection of COVID-19 vaccine.

Despite the fact that the observed lesions were highly characteristic of COVID toes, its clinical presentation may be mistaken for peripheral embolism, or systemic vasculitis.

To our knowledge, COVID toes-like syndrome linked to COVID-19's vaccine has never been previously reported. While chilblain-like lesions in COVID-19 showed features in common with those reported in idiopathic and autoimmune-related chilblains,³ the exact pathophysiology remains unclear. Some could argue for the role of circulating immune complexes. Therefore, she was advised to initiate an anticoagulant therapy (apixaban) and low-dose aspirin until circulating immune complexes were obtained ($<3 \mu\text{g Eq/mL}$) after 14 days, prompting discontinuation of treatments. In fact, COVID toes may be related to microvasculitis (endothelial lesions, micro-thrombosis, fibrin and immune-reactant deposits on vessels), with lymphocytic infiltrate (predominantly CD3/CD4+).⁴ In addition, it has been shown that SARS-CoV-2 could induce vascular damages, with spike protein found in capillary endothelial cells of the upper dermis in a series of 7 patients in pediatrics,⁵ pleading for the same phenomena in the present case.

Four-weeks after vaccination, she remained totally asymptomatic and afebrile, except for one remaining chilblain-like lesion deemed to last a long time (until 150 days).³ Balancing the possible link between vaccination and the observed chilblain-like toes, we decided to contraindicate the second dose of vaccine considering she was at risk of relapsing with further vascular symptoms.

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Contributors' Statement:

BD, PDT and HM conceptualized and designed the manuscript, coordinated and supervised data collection, drafted the initial manuscript, and reviewed the manuscript. BD was in charge of the Figure. MFB and KJ reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



Figure legend: Non-painful violaceous lesions on the big toe, the 3th toe and the left-side of the 4th toe, compatible with the so-called “COVID toes”

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