

COVID-19 Toes and Other Skin Lesions During the Pandemic: Emerging Entities?

Prashanth R. J. Vas, FRCP, PhD^{1,2} ,
George S. Georgiadis, MD, PhD³ ,
and Nikolaos Papanas, MD, PhD⁴ 

The International Journal of Lower
Extremity Wounds
2022, Vol. 21(4) 658–660
© The Author(s) 2021



Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/15347346211011843
journals.sagepub.com/home/ijl



Abstract

There is accumulating evidence to indicate an association between coronavirus infectious disease 2019 (COVID-19) and clusters of incident cutaneous eruptions. Of these, chilblains-like perniosis have received widespread medical and media attention. These typically affect the toes, and have been called “COVID-toes.” Other acral lesions such as large bullae have also been reported. However, a definitive causal relationship with the severe acute respiratory syndrome coronavirus 2 has not yet been definitively proven, nor has a pathogenic mechanism been established. These episodes are self-limiting, but we need to know whether long-term sequelae exist.

Keywords

COVID-19, coronavirus, cutaneous, perniosis

Editorial

The coronavirus infectious disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is predominantly a respiratory tract infection characterized by high infection rate, pulmonary infiltrates, and high mortality among older and immunocompromised individuals.¹ Although the lungs and the immune system are primarily affected, it is now apparent that the virus may also affect other systems, frequently involving the cardiovascular, gastrointestinal tract, and nervous systems.² Inflammation in these is linked with circulatory impairments in the local microvasculature, manifesting as thrombosis in the pulmonary circulation,³ and other parts of the vascular tree.^{4,5} These are accompanied by hypercoagulability⁶ along with increased blood neutrophils and neutrophil extracellular traps.⁷ On histopathological examination, endothelial inflammation and diffuse microvascular necrosis have been noted.^{2,3,8}

Importantly, there are also cutaneous manifestations of COVID-19, first described in an Italian cohort of hospitalized patients. These appear to include maculopapular, urticarial, and vesicular rashes, which may be generalized.⁹ However, the most reported cutaneous feature is the chilblain-like perniosis in the distal parts of the lower extremities, particularly in the feet, the so-called “COVID-toes.”¹⁰⁻¹² Such perniosis was first reported in children and young individuals, but it may be encountered

in all ages.^{10,11} Medical reports of the so-called “clusters of pernio” have received significant attention and wide publicity.¹² Of interest, most individuals with COVID-toes only had mild respiratory symptoms, frequently presenting only with these cutaneous lesions.^{9,11}

Zinder et al¹³ have reported 3 cases of lower extremity bullae in patients hospitalized with severe COVID-19. All patients had serious comorbidities, including diabetes mellitus, obesity, renal dysfunction, cardiac failure, and others.¹³ The bullae resolved with supportive wound care and did not impact their overall clinical course and outcomes.

Importantly, the skin not only provides protection to tissues underneath, but it is also the largest microvascular bed. Cutaneous structures (endothelium, small vessel smooth muscles, and sebaceous glands) express the

¹King's College NHS Foundation Trust, London, UK

²King's Health Partners' Institute of Diabetes, Endocrinology and Obesity, London, UK

³Department of Vascular Surgery, Democritus University of Thrace, University Hospital of Alexandroupolis, Thrace, Greece

⁴Diabetes Centre-Diabetic Foot Clinic, Democritus University of Thrace, Alexandroupolis, Greece

Corresponding Author:

Nikolaos Papanas, Diabetes Centre and Diabetic Foot Clinic, Second Department of Internal Medicine, Democritus University of Thrace, University Hospital of Alexandroupolis, Alexandroupolis 68132, Greece.
Email: papanasnikos@yahoo.gr

angiotensin-converting enzyme-2 (ACE-2) receptor, used by the virus for cell entry.¹⁴ Hence, it is plausible that cutaneous lesions are a direct manifestation of virus-induced microvascular inflammation. However, in many studies, the association with SARS-CoV-2 has been circumstantial or uncertain, perhaps partly attributable to diagnostic shortcomings of viral diagnostic assays.⁹ Certainly, the absence of cold exposure points to a diagnosis other than classical perniosis, encouraging the investigation of new causes.¹⁵

In this context, several questions need to be answered. First, we need to provide a definitive answer on the probable causality. Second, we need to know whether similar or other skin lesions may occur during future waves of the pandemic. Moreover, an inquiry into patient characteristics and comorbidities predisposing to skin lesions is desirable. At present, such perniosis appears to be self-limiting with spontaneous recovery and without any short-term sequelae, but medium- and long-term outcomes are yet to be determined. Additionally, we should decipher if COVID-toes are associated with lung inflammation and/or fibrosis, as well as with systemic endothelial injury, as in perniosis associated with connective tissue disorders.¹⁶

Finally, improved insights into the underlying mechanisms are warranted. There is histopathological evidence of direct microvascular inflammation analogous to pulmonary lesions,^{8,17} but this has not been consistent.¹¹ Indeed, pre-existing endothelial dysfunction may complicate the clinical course and contribute to disproportionate hypoxia in older individuals and those with diabetes and obesity.^{18,19} Still, it is unclear whether such perturbations underlie perniosis. Definitely, they cannot explain the higher frequency of COVID-toes in young adults. As dedicated to the science of wound healing,^{20,21} this journal will seek to contribute to further knowledge.

In conclusion, emerging evidence indicates an association between COVID-19 and clusters of incident cutaneous eruptions, especially perniosis. These most commonly affect the toes. However, the causal relationship has not yet been definitively proven. Indeed, we need to know more about the accuracy of viral tests and the role of patient comorbidities. Meanwhile, however, such lesions should trigger immediate self-isolation and urgent investigation for COVID-19, even in the absence of classical symptoms.

Declaration of Conflicting Interests


The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.


Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Prashanth R. J. Vas  <https://orcid.org/0000-0001-7448-2995>

George S. Georgiadis  <https://orcid.org/0000-0003-1274-3445>

Nikolaos Papanas  <https://orcid.org/0000-0002-7320-785X>

References

- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054-1062.
- Deshmukh V, Motwani R, Kumar A, Kumari C, Raza K. Histopathological observations in COVID-19: a systematic review. *J Clin Pathol*. 2021;74:76-83.
- Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. *N Engl J Med*. 2020;383:120-128.
- Gonzalez Cañas E, Gimenez Gaibar A, Rodriguez Lorenzo L, et al. Acute peripheral arterial thrombosis in COVID-19. Role of endothelial inflammation. *Br J Surg*. 2020;107:e444-e445.
- Cheruiyot I, Kipkorir V, Ngure B, Misiani M, Munguti J, Ogeng'o J. Arterial thrombosis in coronavirus disease 2019 patients: a rapid systematic review. *Ann Vasc Surg*. 2021;70:273-281.
- Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. *J Thromb Haemost*. 2020;18:1559-1561.
- Zuo Y, Yalavarthi S, Shi H, et al. Neutrophil extracellular traps in COVID-19. *JCI Insight*. 2020;5:e138999.
- Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395:1417-1418.
- Singh H, Kaur H, Singh K, Sen CK. Cutaneous manifestations of COVID-19: a systematic review. *Adv Wound Care (New Rochelle)*. 2021;10:51-80.
- Zaladonis A, Huang S, Hsu S. COVID toes or pernio? *Clin Dermatol*. 2020;38:764-767.
- Freeman EE, McMahon DE, Lipoff JB, et al. Pernio-like skin lesions associated with COVID-19: a case series of 318 patients from 8 countries. *J Am Acad Dermatol*. 2020;83:486-492.
- Massey PR, Jones KM. Going viral: a brief history of chilblain-like skin lesions ("COVID toes") amidst the COVID-19 pandemic. *Semin Oncol*. 2020;47:330-334.
- Zinder R, Andrews C, Cristallo J, Flattau A. COVID-19 wounds: unusual lower extremity bullae. *Int J Low Extrem Wounds*. 2020;1534734620964284.
- Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. 2004;203:631-637.
- Herman A, Peeters C, Verroken A, et al. Evaluation of chilblains as a manifestation of the COVID-19 pandemic. *JAMA Dermatol*. 2020;156:998-1003.

16. Takci Z, Vahaboglu G, Eksioglu H. Epidemiological patterns of perniosis, and its association with systemic disorder. *Clin Exp Dermatol*. 2012;37:844-849.
17. Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. *Transl Res*. 2020;220:1-13.
18. Vas P, Hopkins D, Feher M, Rubino F, Whyte MB. Diabetes, obesity and COVID-19: a complex interplay. *Diabetes Obes Metab*. 2020;22:1892-1896.
19. Whyte MB, Vas P, Heiss C, Feher MD. The contribution of diabetic micro-angiopathy to adverse outcomes in COVID-19. *Diabetes Res Clin Pract*. 2020;164:108217.
20. Papanas N, Papi M, Rerkasem K. Progress in wound healing: wisdom not consumed in confidence? *Int J Low Extrem Wounds*. 2019;18:5.
21. Papanas N, Papi M, Rerkasem K. The science of wound healing: perhaps, "more lovely and more temperate"? *Int J Low Extrem Wounds*. 2019;18:110-111.