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Caution in the time of rashes and COVID-19

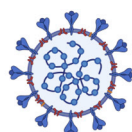


To the Editor: We applaud the authors of a recent report in *JAAD*¹ who performed a systematic literature review of the highly variable cutaneous manifestations of coronavirus disease 2019 (COVID-19). Since the global pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), dermatologists have mobilized to identify, catalog, and disseminate potential cutaneous manifestations of SARS-CoV-2 infection. Lack of widespread testing and potential limitations in assays that detect acute and previous infections underscore the utility of identifying skin manifestations of COVID-19.

These limitations, however, make it difficult to definitively conclude that skin manifestations of

COVID-19 are due to SARS-CoV-2. In fact, the most commonly reported cutaneous manifestation, pernio-like lesions (so-called COVID toes),¹ seem to generally occur in patients who test negative for viral infection by polymerase chain reaction and subsequent serologic testing.² However, detection of SARS-CoV-2 in endothelial cells of these lesions suggests direct viral invasion.³

On the other hand, patients who have confirmed SARS-CoV-2 infection have been reported to develop a wide variety of cutaneous manifestations, including morbilliform eruption, urticaria, petechiae, retiform purpura, periorbital erythema, vesicular, livedo reticularis, digitate papulosquamous, erythema multiforme, pernio-like lesions, and androgenic alopecia¹⁻³ (Fig 1). It remains to be determined which skin manifestations are a sign of



Reported Cutaneous Manifestations of COVID-19

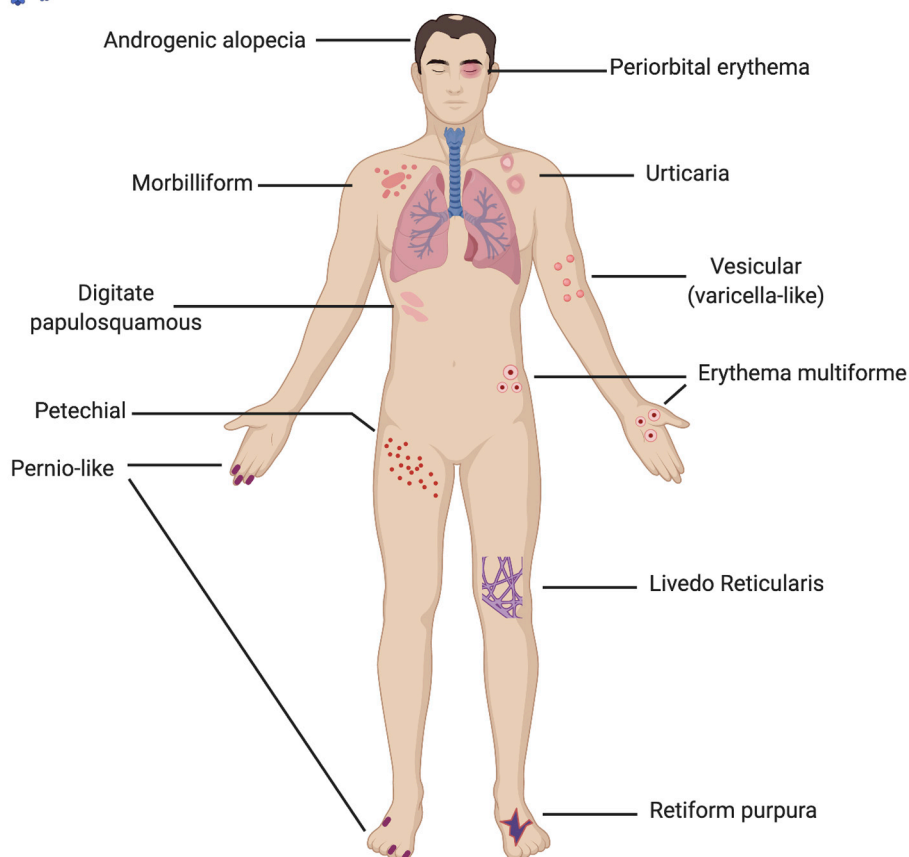


Fig 1. Reported cutaneous manifestations of coronavirus disease (COVID-19). These skin findings have been reported by clinicians as potential signs of COVID-19. Most of these highly variable and rare findings reported in case reports and small case series may not be specific to severe acute respiratory syndrome coronavirus 2 infection. We urge caution and continued scholarship moving forward to decipher what impact COVID-19 has on skin.

SARS-CoV-2 infection due to direct tissue injury from viral tropism or to sequela of infection such as coagulopathy and immune injury.³

We recommend caution when concluding that cutaneous findings are specifically due to SARS-CoV-2. Without question, SARS-CoV-2 is a unique and devastating virus with multiple tissue tropism and heterogeneous immune activation. With further clinical studies, more widespread testing, and a better understanding of the natural course of the virus, these skin manifestations will likely settle into 2 types: virus-specific and nonspecific. To determine virus-specific mechanisms, direct detection of viral particles within cutaneous lesions is needed.³ Furthermore, these studies should use control tissue of similar lesions (eg, perniosis) that occurred before the pandemic.

In the absence of direct viral detection, unique immune signatures identified within patients with COVID-19 should be investigated in patients who develop skin manifestations. Cutaneous lesions that are nonspecific should be grouped into those that are suggestive of COVID-19 vs those that are not. The COVID-19 Dermatology Registry will be critical to identifying which cutaneous manifestations are most suggestive of COVID-19.

The difficulty in classifying the cutaneous manifestations of a systemic, complex, and heterogeneous immune-mediated disease is reminiscent of systemic lupus erythematosus (SLE). Although distinct in etiology, disease course, and treatment, the lessons learned from studying SLE may be applied to understanding the cutaneous manifestations of COVID-19. In 1992, Dr Robert A. Greenwald commented that “anything happening to a patient with SLE which is not immediately otherwise explicable will automatically be blamed on the lupus, regardless of pathophysiological validity.”⁴ This became known as Greenwald’s law of lupus. Subsequently, Dr Richard Sontheimer provided a corollary to Greenwald’s law that anything happening to patient with a positive anti-nuclear antibody will be blamed on lupus.⁵ Now it appears that anything happening to a patient’s skin during the COVID-19 pandemic will be attributed to SARS-CoV-2 infection, rightly or wrongly.

We thank Dr Jean Bologna for input on the figure. [Biorender.com](https://www.biorender.com) was used to generate the figure with academic subscription.

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Funding sources: Dr Vesely is supported by the Dermatology Foundation, the Melanoma Research Alliance, and National Institutes of Health National Center for Advancing Translational Sciences (KL2-TR-001862).

Conflicts of interest: None disclosed.

IRB approval status: Not applicable.

Reprints not available from the authors.

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REFERENCES

1. Jia JL, Kamceva M, Rao SA, Linos E. Cutaneous manifestations of COVID-19: a preliminary review. *J Am Acad Dermatol*. 2020; 83(2):687-690.
2. Galvan Casas C, Catala A, Carretero Hernandez G, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. *Br J Dermatol*. 2020;183(1):71-77.
3. Colmenero I, Santonja C, Alonso-Riano M, et al. SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of 7 paediatric cases [e-pub ahead of print]. *Br J Dermatol*; 2020. <https://doi.org/10.1111/bjd.19327>. Accessed July 1, 2020.
4. Greenwald RA. Greenwald’s law of lupus. *J Rheumatol*. 1992; 19(9):1490.
5. Sontheimer RD. Greenwald’s law of lupus: the Sontheimer amendment. *J Rheumatol*. 1993;20(7):1258-1259.

<https://doi.org/10.1016/j.jaad.2020.07.026>