"COVID toes": A true viral phenomenon or a diagnosis without a leg to stand on?

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"COVID toes" is the colloquial name of chilblain-like lesions thought to be a sequela of COVID-19 infection. Over two years and approximately 300 publications later, this association remains controversial. Here, we summarize key clinical, serological, biological, histological, and immunological evidence that supports and rejects this relationship and discuss alternate theories underlying the pathogenesis of chilblain-like lesions. (JAAD Int 2022;9:■-■.)

Key words: acral lesions; acro-ischemia; chilblain-like lesions (CBLL); chilblains; coronavirus; COVID-19; COVID toes; cutaneous vasculitis; Epstein-Barr virus (EBV); factor V Leiden; humoral immunity; infection; interferon (IFN); lipoprotein A; pandemic; pernio; postacute sequelae of COVID-19 (PASC); pseudo-chilblains; skin of color; vaccine; virus.

CLINICAL

Emergence and temporal association of chilblain-like lesions (CBLLs) with the arrival of COVID-19

The initial publication from China on the first surge of COVID-19 cases had no reports of CBLLs, and only two out of 1099 patients were described as having any cutaneous findings (rash).[1] However, the severe pulmonary manifestations associated with COVID-19 infection were more likely the critical focus at that time. Reports of "COVID toes" first emerged from Europe when they had a peak of coronavirus infections.[2-4] Subsequently, the diagnosis was disseminated on social media. Nonetheless, multiple studies involving large cohorts of COVID-19–infected patients in heavily impacted "surge" areas, such as New York City, New York, United States, and Sao Paolo, Brazil, failed to detect a similarly increased incidence of this finding.[5-7] In another large epidemiologic study from California, United States, McCleskey et al[8] did find an increase in the number of cases of chilblains during the pandemic, but these cases had a low correlation with hot spots where COVID-19 infections were identified.

Geographic and racial distribution

In the United States, the lack of reports of CBLLs specifically in individuals with darker skin generated a significant amount of controversy, with the absence of representative imagery of this finding in patients with Fitzpatrick type V skin highlighted in the media as evidence of a deficiency in dermatologic training.[9,10] Interestingly, however, in a study from India, Pangti et al[11] reported that cutaneous manifestations were similarly uncommon in pigmented skin in a series of patients with confirmed COVID-19 diagnoses.

Apart from differences in reports of CBLLs by race, geography seemed to play a role, with an overwhelming number of cases derived from Europe and North America and scant reports from Asia.[12,13] By way of explanation, one hypothesis linked the development of CBLLs to the variable distribution of molecular factors associated with thromboembolic activity among disparate populations. Lipoprotein A and Factor V Leiden are critical players in thrombo-occlusive vasculopathies. Compared with Asians, Caucasians are thought to have a higher incidence of Factor V Leiden mutations and higher levels of lipoprotein A. This increased predisposition

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to thrombophilia may have contributed to the differences in the prevalence of CBLLs as a by-product of COVID-19 infection across geographic regions.[14,15]

The variable presence of this finding by race and geography is notable. This may be accounted for by underlying predispositions to thromboembolic events in certain populations and other factors such as physician biases and/or patient (self-reporting) biases in dermatologic diagnosis. Conversely, this discrepancy may underscore the tenuous nature of this association and the inherent presence of selection biases in the evaluation of this condition.

CAPSULE SUMMARY

- "COVID toes" is the colloquial name of chilblain-like lesions, which are thought to be a sequela of COVID-19 infection. Over two years and approximately 300 publications later, this association remains controversial.
- Here, we summarize key clinical, serological, biologicalal, histological, and immunological evidence that supports and rejects this relationship.

Presentation

The cutaneous presentation of COVID-19 infection is highly variable, encompassing a wide range of skin findings, including vesiculobullous lesions, exanthematous eruptions, livedoid presentations, and necrotic plaques, in addition to CBLLs.[12] The proposed incidence of skin manifestations associated with COVID-19 is unknown and can vary dramatically, ranging from 0.2% to 20.4% of cases, according to some published reports.[16]

In a large smartphone application-based survey study of >300,000 subjects in the United Kingdom, Visconti et al[17] noted a significant association between rashes and positive COVID-19 swab results (odds ratio, 1.67; 95% CI, 1.42-1.97). In 17% of COVID-19–positive cases, cutaneous symptoms were the first presentation of the disease, and in 21% of cases, skin and acral lesions were the only clinical manifestations of COVID-19 infection. Moreover, the odds ratio for rashes (1.67) was greater than that for fever (1.48), a widely accepted indication for COVID-19 testing, thus suggesting that cutaneous symptoms can be predictive of COVID-19 infection.[17]

The incidence of CBLLs specifically is difficult to ascertain because it is a rare phenomenon relative to COVID-19 infection. However, a rate of 28.6 per 100,000 person-years during the pandemic, compared with 5.2 per 100,000 person-years prior to the pandemic, was reported in one study from northern California, United States.[8] CBLLs are thought to have a particular demographic predilection, most commonly found in young, healthy patients who are otherwise asymptomatic or have a mild disease course. These CBLLs may often be indistinguishable from classic chilblains but are distinct from the acroischemic lesions that more commonly affect older or immunocompromized individuals with an increased risk of severe systemic symptoms and a higher likelihood of hospitalization.[3,18]

BIOLOGICAL, IMMUNOLOGIC, AND SEROLOGIC EVIDENCE OF COVID-19 INFECTION

Polymerase chain reaction as well as immunoglobulin (Ig)G and IgM immunostaining

Laboratory confirmation of the association of CBLLs with COVID-19 has been confounded by the fact that these "well" patients often tested negative for active COVID-19 infection using reverse transcriptase polymerase chain reaction (RT-PCR) at the time of presentation. Thus, it was largely concluded that CBLLs are likely a late manifestation that occur 1 to 4 weeks after the infection.[13,19] Complicating the matter, unlike patients with more severe disease, patients with CBLLs frequently did not produce IgM or IgG antibodies indicative of prior COVID-19 infection.[19] However, these individuals were routinely only tested at a single point in time, which may not have reflected the entire immune response. The absence of clinical symptomology in conjunction with the lack of confirmatory biological or serologic evidence of infection in many of these patients supported the conjecture that the development of CBLLs was an epiphenomenon unrelated to direct infection with the virus.

IgA immunostaining

As a counter argument, El Hachem et al[20] suggested that the presence of IgA serology for COVID-19, observed in several patients who failed to demonstrate anti-COVID-19 IgG positivity, is a more useful marker of infection with a respiratory virus because it is the most concentrated isotype at mucosal sites. In a series of 40 patients with CBLLs, Hubiche et al[18] also observed that positive IgA serology for SARS-CoV-2 was detected more often. Although all 40 patients tested negative using RT-PCR, 12 (30%) had positive serologic results, with 8 (20%) testing positive for anti-COVID-19 IgA antibodies. Of those 8 patients, 7 (87.5%) tested positive

Abbreviations used:

CBLL:	chilblain-like lesion
EBV:	Epstein-Barr virus
IFN:	interferon
Ig:	immunoglobulin
RT-PCR:	reverse transcriptase polymerase chain reaction

exclusively for IgA but negative for IgG and IgM.[18,21] While anti-SARS-CoV-2 IgA may be a more sensitive marker of asymptomatic and mild infections, it is rarely used in the commercial laboratory setting.

HISTOLOGIC EVIDENCE OF THE SARS-COV-2 VIRUS IN BIOPSY SPECIMENS

Immunohistochemistry

To establish whether CBLLs are a direct result of viral infection, immunostaining was performed on biopsied specimens. Using a monoclonal antibody against the spike protein of SARS-CoV-2, Colmenero et al[22] detected the virus in all samples of CBLLs in a series of patients. However, when this approach was attempted using an antibody against the nucleocapsid portion of SARS-CoV-2 in another case series, no virus was found, suggesting that the prior study's staining was possibly nonspecific.[23]

In situ hybridization

As the gold standard for detection, RT-PCR and in situ hybridization were used on CBLL specimens obtained from adolescents, and again, the viral genome was not identified.[19,24] This important finding largely confirmed that CBLLs are unlikely to be infectious. However, using RT-PCR, the virus was detected in the flank of a woman with a macular eruption and symptoms suspicious for COVID-19, suggesting that COVID-19 can be potentially be found in the skin.[25]

THEORIES OF PATHOGENESIS

Type I interferon response

In some patients with chilblains, high levels of type I interferon (IFN), a critical player in the innate immune response, were identified.[26] This is consistent with the aforementioned study by Hubiche et al,[18] in which the levels of IFN-α were significantly elevated in patients with CBLLs, all of whom had mild disease, compared with those in patients with moderate or severe COVID-19 infection. Accordingly, an association between impaired type I IFN and severe COVID-19 has also been identified.[27,28] Taken together, these findings support the hypothesis that an exuberant immune response in healthy people might trigger CBLLs while efficiently clearing the virus before the humoral immune response can occur.[29]

Gehlhausen et al[30] countered this hypothesis by noting that elevated IFN levels are not uniquely associated with CBLLs. An IFN response can also be observed in patients with chilblains lupus, and the induction of type I IFN is an important part of the host's innate immune response to common viral infections, such as Epstein-Barr virus (EBV), also linked to chilblains.[30-32] Thus, the activation of the IFN signaling pathway does not preclude a variety of causes of chilblains that may present similarly.

Several reports identifying CBLLs shortly after COVID-19 vaccination with the Moderna or Pfizer-BioNTech vaccines have emerged.[33-38] In these case reports, CBLLs most commonly appeared within 1 week of inoculation with a messenger RNA COVID-19 vaccine. Serologic testing in these individuals demonstrated the presence of IgG antibodies against the spike protein and the absence of antibodies against the nucleocapsid protein; revealing that there was no concurrent natural infection. These vaccination-associated cases coupled with evidence of type I IFN involvement in blood and lesional biopsy samples lent further credence to the idea that CBLLs are a sequela of an immunological response to COVID-19.[35,36] Nonetheless, new-onset or resurgence of autoimmunity after vaccination is a well-established (albeit uncommon) phenomenon, and thus, the rare incidence of CBLLs after vaccination may also not be specific to COVID-19.[38]

Viral reactivation

CBLLs have also been identified in patients who experience a more protracted disease course, known as postacute sequelae of COVID-19 or so-called "long-haulers."[39] Not uncommonly, patients suffering from prolonged symptoms of COVID-19 infection had only a minor illness and were not hospitalized. Interestingly, according to Gold et al,[40] a large percentage (66.7%) of these subjects were found to have evidence of EBV reactivation. Moreover, simultaneous infection due to cytomegalovirus and/or EBV as well as SARS-CoV-2 in the presence of CBLLs has been reported.[41] Notably, Su et al[42] found the coexistence of EBV and SARS-CoV-2 viremia detected at the time of clinical diagnosis to be predictive of postacute sequelae of COVID-19 up to 3 months later. As such, COVID-19–related symptoms could be a byproduct of inflammation-driven EBV reactivation subsequent to SARS-CoV-2 infection rather than a direct effect of the coronavirus itself.[40,42,43]

Table I. Summary of key data supporting and rejecting the association of COVID toes with COVID-19 infection

Variable	Evidence of association with COVID-19	No evidence of association with COVID-19
Clinical		
Temporal association of an outbreak of CBLLs with the arrival of COVID-19	Reports from Europe documented increased cases of CBLLs concurrent with a surge of COVID-19.[2-4]	Studies from other heavily impacted areas, such as New York City and Sao Paolo, found no increased incidence or paucity of cases of CBLLs concurrent with similar surges of COVID-19.[5-7]
Geographic and racial distribution of cases of CBLLs	CBLLs were the most common cutaneous manifestation associated with COVID-19 in Europe and the United States, with cases overwhelmingly reported in Caucasian patients.[8,9,12]	Conspicuously few cases of CBLLs have been documented in Asia, and there is a paucity of cases identified in patients with skin of color.[5-7,11,12]
Clinical presentation suggestive of COVID-19 infection in patients with CBLLs	Reports of patients with CBLLs having concurrent and/or prior upper respiratory infection symptoms or illness suggestive of COVID-19.[17,18,44] Skin and acral rashes were predictive of COVID-19 infection in a large survey study.[17]	Patients with CBLLs often report no prior systemic symptoms and are commonly asymptomatic at the time of infection, clinically, not suggestive of a concurrent or prior infectious process.[13,19]
Biological		
Laboratory evidence of COVID-19 infection coincident with the presentation of CBLLs	CBLLs have been identified after PCR-diagnosed infection due to SARS-CoV2.[44]	RT-PCR for active COVID-19 infection (nasopharyngeal swab) is commonly negative in patients with CBLLs at the time of presentation, and many patients with CBLLs never tested positive for the virus.[19]
Immunologic/serologic		
Evidence of prior COVID-19 infection	Development of anti-SARS-CoV-2 IgA in up to 20% of cases of CBLLs.[18,20,21]	Commercially available antibodies indicative of prior COVID-19 infection (IgG and IgM) are often undetectable in cases of CBLL.[19]
Histologic		
Immunostaining	A monoclonal antibody against the spike protein of SARS-CoV-2 detected the virus in biopsied samples of CBLLs.[22]	Biopsies of CBLLs stained with antibodies against the nucleocapsid protein of SARS-CoV-2 failed to detect the virus.[23]
Genomic evidence of COVID-19 in the skin	SARS-CoV-2 was detectable at low copy numbers using PCR on a biopsied rash from the flank of an adult woman with symptoms suspicious for COVID-19.[25]	SARS-CoV-2 RNA has been undetectable using RT-PCR and in situ hybridization in biopsied samples of CBLLs.[19,24]
Theories of pathogenesis		
Type I IFN immune response/ viral reactivation	IFN-α levels were significantly elevated in some patients with CBLLs, all of whom had mild disease.[13,18,24,26]	An increased IFN response has also been observed in patients with chilblains lupus, and the induction of type I IFN is an important part of the host's innate immune response to common viral infections such as EBV, which is also linked to the development of chilblains.[31,32]

CBLL, Chilblain-like lesion; *EBV*, Epstein-Barr virus; *IFN*, interferon; *IgA*, immunoglobulin A; *IgG*, immunoglobulin G; *IgM*, immunoglobulin M; *PCR*, polymerase chain reaction; *RT-PCR*, reverse transcriptase polymerase chain reaction.

CONCLUSION

CBLLs are arguably the most well-publicized cutaneous manifestation of the pandemic (Table I) and have alternately been described as an important sign of infection, a social media phenomenon, a consequence of selection bias, an immunologically mediated viral reaction, or a result of quarantine-related behavioral change. It is now abundantly clear that testing can miss many cases of infection and that antibodies manifestly wane over time, confounding laboratory evidence of a direct link between CBLLs and the virus. Nevertheless, reports of CBLLs remain

relatively rare in the context of overwhelming COVID-19 infection, suggesting that the association between these 2 conditions is unlikely to be a strong one.

To date, many uncertainties remain, and new questions, such as the persistence of this finding in the presence of novel variants, have emerged. Inquiry spurred on by the pandemic has already advanced our understanding of the pathophysiology of chilblains.[23] Further investigation will continue to clarify the pathogenesis of cutaneous manifestations associated with the immune response to COVID-19 infection.

Conflicts of interest

None disclosed.

REFERENCES

1. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720.
2. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. *J Eur Acad Dermatol Venereol*. 2020;34(5):e212-e213.
3. Fernandez-Nieto D, Jimenez-Cauhe J, Suarez-Valle A, et al. Characterization of acute acral skin lesions in nonhospitalized patients: a case series of 132 patients during the COVID-19 outbreak. *J Am Acad Dermatol*. 2020;83(1):e61-e63.
4. Galván Casas C, Catala AC, Carretero Hernández 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.
5. Cline A, Berk-Krauss J, Jacobs AK, et al. The underrepresentation of "COVID toes" in skin of color: an example of racial bias or evidence of a tenuous disease association? *J Am Acad Dermatol*. 2021;84(2):e91-e92.
6. Avancini J, Miyamoto D, Arnone M, et al. Absence of specific cutaneous manifestations of severe acute respiratory syndrome coronavirus 2 in a reference center in Brazil. *J Am Acad Dermatol*. 2021;84(1):e67.
7. Deutsch A, Blasiak R, Keyes A, et al. COVID toes: phenomenon or epiphenomenon? *J Am Acad Dermatol*. 2020;83(5):e347-e348.
8. McCleskey PE, Zimmerman B, Lieberman A, et al. Epidemiologic analysis of chilblains cohorts before and during the COVID-19 pandemic. *JAMA Dermatol*. 2021;157(8):947-953.
9. Rabin RC. Dermatology has a problem with skin color. New York Times. Accessed January 10, 2022. https://www.nytimes.com/2020/08/30/health/skin-diseases-black-hispanic.html
10. Lipper GM. COVID-19-related skin changes: the hidden racism in documentation. Medscape. Updated July 27, 2020. Accessed January 15, 2020. https://www.medscape.com/viewarticle/934605
11. Pangti R, Gupta S, Nischal N, Trikha A. Recognizable vascular skin manifestations of SARS-CoV-2 (COVID-19) infection are uncommon in patients with darker skin phototypes. *Clin Exp Dermatol*. 2021;46(1):180-182.
12. Tan SW, Tam YC, Oh CC. Skin manifestations of COVID-19: a worldwide review. *JAAD Int*. 2021;2:119-133.
13. Baeck M, Herman A. COVID toes: where do we stand with the current evidence? *Int J Infect Dis*. 2021;102:53-55.
14. Criado PR, Abdalla BM, de Assis IC, van Blarcum de Graaff Mello C, Caputo GC, Vieira IC. Are the cutaneous manifestations during or due to SARS-CoV-2 infection/COVID-19 frequent or not? Revision of possible pathophysiologic mechanisms. *Inflamm Res*. 2020;69(8):745-756.
15. Desai SR, McMichael AJ, Khanna R. Coronavirus disease 2019 and race in dermatology. *Dermatol Clin*. 2021;39(4):569-574.
16. Feldman SR, Freeman EE. COVID-19: cutaneous manifestations and issues related to dermatologic care. UptoDate. Updated October 22, 2021. Accessed January 12, 2022. https://www.uptodate.com/contents/covid-19-cutaneous-manifestations-and-issues-related-to-dermatologic-care
17. Visconti A, Bataille V, Rossi N, et al. Diagnostic value of cutaneous manifestation of SARS-CoV-2 infection. *Br J Dermatol*. 2021;184(5):880-887.
18. Hubiche T, Cardot-Leccia N, Le Duff F, et al. Clinical, laboratory, and interferon-alpha response characteristics of patients with chilblain-like lesions during the COVID-19 pandemic. *JAMA Dermatol*. 2021;157(2):202-206.
19. Herman A, Peeters C, Verroken A, et al. Evaluation of chilblains as a manifestation of the COVID-19 pandemic. *JAMA Dermatol*. 2020;156(9):998-1003.
20. El Hachem M, Diociaiuti A, Concato C, et al. A clinical, histopathological and laboratory study of 19 consecutive Italian paediatric patients with chilblain-like lesions: lights and shadows on the relationship with COVID-19 infection. *J Eur Acad Dermatol Venereol*. 2020;34(11):2620-2629.
21. Hubiche T, Le Duff F, Chiaverini C, Giordanengo V, Passeron T. Negative SARS-CoV-2 PCR in patients with chilblain-like lesions. *Lancet Infectious Dis*. 2021;21(3):315-316.
22. Colmenero I, Santonja C, Alonso-Riaño M, et al. SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven paediatric cases. *Br J Dermatol*. 2020;183(4):729-737.
23. Ko CJ, Harigopal M, Damsky W, et al. Perniosis during the COVID-19 pandemic: Negative anti-SARS-CoV-2 immunohistochemistry in six patients and comparison to perniosis before the emergence of SARS-CoV-2. *J Cutan Pathol*. 2020;47(11):997-1002.
24. Discepolo V, Catzola A, Pierri L, et al. Bilateral Chilblain-like lesions of the toes characterized by microvascular remodeling in adolescents during the COVID-19 pandemic. *JAMA Network Open*. 2021;4(6):e2111369.
25. Jamiolkowski D, Mühleisen B, Müller S, Navarini AA, Tzankov A, Roider E. SARS-CoV-2 PCR testing of skin for COVID-19 diagnostics: a case report. *Lancet*. 2020;396(10251):598-599.
26. Frumholtz L, Bouaziz JD, Battistella M, et al. Type I interferon response and vascular alteration in chilblain-like lesions during the COVID-19 outbreak. *Br J Dermatol*. 2021;185(6):1176-1185.
27. Trouillet-Assant S, Viel S, Gaymard A, et al. Type I IFN immunoprofiling in COVID-19 patients. *J Allergy Clin Immunol*. 2020;146(1):206-208.
28. Hadjadj J, Yatim N, Barnabei L, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science*. 2020;369(6504):718-724.
29. Damsky W, Peterson D, King B. When interferon tiptoes through COVID-19: pernio-like lesions and their prognostic implications during SARS-CoV-2 infection. *J Am Acad Dermatol*. 2020;83(3):e269-e270.
30. Gehlhausen JR, Little AJ, Ko CJ, et al. Lack of association between pandemic chilblains and SARS-CoV-2 infection. *Proc Natl Acad Sci USA*. 2022;119(9):e2122090119.
31. Battesti G, El Khalifa J, Abdelhedi N, et al. New insights in COVID-19-associated chilblains: a comparative study with

chilblain lupus erythematosus. *J Am Acad Dermatol*. 2020; 83(4):1219-1222.
32. Liu X, Sadaoka T, Krogmann T, Cohen JI. Epstein-Barr virus (EBV) tegument protein BGLF2 suppresses type I interferon signaling to promote EBV reactivation. *J Virol*. 2020;94(11): e00258-20.
33. Kelso JM, Coda AB, Keating RM, Vaccari DM. "COVID Toes" after mRNA COVID-19 vaccines. *J Allergy Clin Immunol Pract*. 2021;9(8):3196-3197.
34. Lesort C, Kanitakis J, Donzier L, Jullien D. Chilblain-like lesions after BNT162b2 mRNA COVID-19 vaccine: a case report suggesting that 'COVID toes' are due to the immune reaction to SARS-CoV-2. *J Eur Acad Dermatol Venereol*. 2021;35(10): e630-e632.
35. Davido B, Mascitti H, Fortier-Beaulieu M, Jaffal K, de Truchis P. 'Blue toes' following vaccination with the BNT162b2 mRNA COVID-19 vaccine. *J Travel Med*. 2021; 28(4):taab024.
36. Souaid K, Oules B, Sohier P, Deschamps L, Aractingi S, Dupin N. Type I interferon signature in chilblains following SARS-CoV-2 mRNA vaccine: a case report. *Acta Derm Venereol*. 2021; 101(11):adv00589.
37. McMahon DE, Amerson E, Rosenbach M, et al. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: a registry-based study of 414 cases. *J Am Acad Dermatol*. 2021;85(1):46-55.
38. Gambichler T, Boms S, Susok L, et al. Cutaneous findings following COVID-19 vaccination: review of world literature and own experience. *J Eur Acad Dermatol Venereol*. 2022;36(2):172-180.
39. Salamon M. Skin symptoms common in COVID 'long-haulers'. Medscape. Updated October 20, 2020. Accessed January 12, 2022. https://www.medscape.com/viewarticle/940058
40. Gold JE, Okyay RA, Licht WE, Hurley DJ. Investigation of long COVID prevalence and its relationship to Epstein-Barr virus reactivation. *Pathogens*. 2021;10(6):763.
41. Sugawara-Mikami M, Ishii N, Yamazaki M, et al. Skin manifestations of suspected COVID-19: complications of the disease or reactivation of latent viral infections? *JAAD Case Rep*. 2021;12:15-17.
42. Su Y, Yuan D, Chen DG, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell*. 2022;185(5):881-895.
43. Belluck P. New research hints at 4 factors that may increase chances of long covid. New York Times. Accessed May 10, 2022. https://www.nytimes.com/2022/01/25/health/long-covid-risk-factors.html
44. 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(2):486-492.