Cutaneous manifestations in COVID-19: Lessons learned from current evidence

To the Editor: The ongoing pandemic of coronavirus disease 2019 (COVID-19) is a significant global concern. As of April 19, 2020, a total of 2,241,359 accumulated cases and 152,551 deaths have been reported worldwide.[1] The clinical features of COVID-19 have been described in several articles. The disease typically presents with symptoms resembling other viral respiratory infections, most commonly with fever and dry cough. Patients with severe infection may later develop acute respiratory distress syndrome that could progress to multiple organ failure with a relatively high mortality rate.[2]

In addition, the disease is associated with leukopenia, thrombocytopenia, and elevated D-dimer levels that increase the risk of venous thromboembolism.[3] Emerging evidence suggests that the uncontrolled release of proinflammatory cytokines resulting in cytokine storm syndrome plays an immunopathogenic role in disease progression and the development of severe disease.[4]

Cutaneous manifestations are considered an infrequent presentation of COVID-19, being rarely described in the literature. They are probably under-recognized due to a lack of dermatology consultations in this group of patients. The first evidence of skin manifestations was reported in 2 patients with severe respiratory disease in a study of 1099 cases in China. However, neither characteristics nor progression of the lesions were documented.[2]

Since then, subsequent case reports and case series have described COVID-19–associated skin lesions in patients with confirmed COVID-19, including clinical features that indicate viral exanthems (ie, morbilliform rash, petechial rash coexisting with thrombocytopenia, erythematous-to-purpuric coalescing macules, widespread urticaria, and varicella-like vesicles) and vasculopathy-related skin manifestations (ie, peripheral cyanosis with bullae and dry gangrene, transient unilateral livedo reticularis, and red papules on fingers resembling chilblains). Other patients with non-laboratory-confirmed COVID-19 showed urticaria and painful erythematous-to-violaceous patches evolving into tense vesicles or dark crusts. All cases reported so far are summarized in Table I.

According to pre-existing data, we can speculate that cutaneous manifestations in COVID-19 may present in 2 major groups regarding their pathomechanisms: (1) clinical features similar to viral exanthems, an immune response to viral nucleotides; and (2) cutaneous eruptions secondary to systemic consequences caused by COVID-19, especially vasculitis and thrombotic vasculopathy. Apart from the above-mentioned, patients with COVID-19 are more likely to have an increased risk of adverse drug reactions and interactions of their treatment causing secondary cutaneous reactions at any point during the course of the disease. Therefore, identifying clues that support a viral cause or drug eruption is essential. Table II summarizes cutaneous reactions reported in proposed drugs for COVID-19 treatment.[5]

In summary, whether skin lesions in patients with COVID-19 are related with the virus remains unclear. Dermatologists should keep in mind that skin eruptions occurring in patients with COVID-19 could result from viral infections, systemic consequences, or prescribed drugs. Early recognition of cutaneous signs that are associated with severe complications and prompt management are essential to improve patient outcomes. Moreover, further clinical studies regarding skin manifestations in COVID-19 are required to comprehend the exact cutaneous features for more accurate diagnoses that may predict disease outcomes in particular patients.

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Table I. Summary of reported COVID-19 cases with cutaneous manifestations between January 1, 2020, and April 19, 2020

Authors*	No.	Age, y and sex	Cutaneous manifestations	Extracutaneous manifestations	Laboratory-confirmed COVID-19 case	Associated with disease severity	Skin biopsy	Progression	Article link
Reported cases with skin manifestations that indicate viral exanthems									
Guan et al	2 of 1099	NA	NA	NA	Yes	Yes	No	NA	https://doi.org/10.1056/NEJMoa2002032
Joob and Wiwanitkit	1	NA	Skin rash with petechiae	Fever, thrombocytopenia, respiratory symptoms	Yes	NA	No	NA	https://doi.org/10.1016/j.jaad.2020.03.036
Recalcati	18 of 88	NA	Erythematous rash (n = 14), widespread urticaria (n = 3), chickenpox-like vesicles (n = 1)	NA	Yes	No	No	NA	https://doi.org/10.1111/jdv.16387
Hunt and Koziatek	1	20, M	Diffuse nonpruritic erythematous morbilliform rash on trunk and extremities	Fever, multifocal pneumonia with decreased oxygen saturation	Yes	Yes	No	NA	https://doi.org/10.5811/cpcem.2020.3.47349
Mahé et al	1	64, F	Erythematous rash on both antecubital fossa, trunk, and axillary folds resembling symmetric drug-related intertriginous and flexural exanthem	Fever, cough, asthenia, bilateral pneumonia	Yes	No	No	Improved within 5 days	https://doi.org/10.1111/jdv.16471
Jimenez-Cauhe et al	1	84, F	Mild pruriginous erythematous-purpuric, coalescing macules on the periaxillary area	Bilateral pneumonia	Yes	NA	No	NA	https://doi.org/10.1016/j.jaad.2020.04.016
Marzano et al	22	8-90; 16M and 6F	Diffuse/scattered papulovesicular lesions on trunk (n = 22) and extremities (n = 4), mild itch (n = 9), pain (n = 2), burning (n = 3)	Fever, cough, headache, weakness, coryza, dyspnea, hyposmia, hypogeusia, pharyngodynia, diarrhea, myalgia	Yes	No	Yes (n = 7)	4-15 days	https://doi.org/10.1016/j.jaad.2020.04.044
Lu et al	1	NA	Urticaria	Bilateral pneumonia with minimal symptom	No	No	No	NA	https://doi.org/10.1002/jmv.25776
Henry et al	1	27, F	Generalized urticaria on face and extremities	Odynophagia, arthralgia, chills, fever, chest pain	Yes	No	No	NA	https://doi.org/10.1111/jdv.16472
Fernandez-Nieto et al	1	32, F	Urticaria	NA	Yes	No	Yes	Improved within 5 days	https://doi.org/10.1111/jdv.16470
Hoehl et al	1 of 2	NA	Faint rash	Minimal pharyngitis	Yes	No	No	NA	https://doi.org/10.1056/NEJMc2001899

Reported cases with vasculopathy-related skin manifestations

Zhang et al	7	49-71; 4 M and 3 F	Finger/toe cyanosis, skin bullae, and dry gangrene	Fever, cough, dyspnea, diarrhea	Yes	Yes	No	NA	https://doi.org/10.3760/cma.j.issn.0253-2727.2020.0006
Mazzotta and Troccoli	1	13, M	Erythematous-violaceous rounded lesions on toes with 1-cm diameter, tense blister, blackish crusts at 7 days later	Low-grade fever, muscle pain, headache	No	No	No	Regressed in 2 weeks	http://sectcv.es/wp-content/uploads/2020/04/acroischemia-ENG.pdf
Manalo et al	2	67, M	Transient nonpruritic blanching unilateral livedoid patch on right thigh	Low-grade fever, nasal congestion, post-nasal drip, cough, hematuria	Yes	Yes	No	Resolved within 19 hours	https://doi.org/10.1016/j.jaad.2020.04.018
		47, F	Unilateral transient asymptomatic rash on right leg resembling livedo reticularis	Low-grade fever, mild headache, sinus pressure, anosmia	Yes	No	No	Resolved within 20 minutes	
Ma et al	1 of 3	69, M	Dry gangrene on right index finger	Fever, bilateral pneumonia, antiphospholipid syndrome with cerebral infarcts	Yes	Yes	No	NA	https://doi.org/10.1016/j.clim.2020.108408
Zhang et al	1 of 3	69, M	Ischemia on both lower limbs and digits of the left hand	Fever, bilateral pneumonia, diarrhea, headache, multiple cerebral infarcts, positive antiphospholipid antibodies	Yes	Yes	No	NA	https://doi.org/10.1056/NEJMc2007575
Alramthan and Aldaraji	2	27 and 35; 2 F	Red-to-purple papules on the dorsal aspects of fingers (n = 2), diffused erythema in the subungual area of the right thumb (n = 1), clinical features resembling chilblains	None	Yes	No	No	NA	https://doi.org/10.1111/ced.14243
Estebanez et al	1	28, F	Confluent erythematous-yellowish papules on both heels, later developed into pruritic erythematous plaques resembling urticarial vasculitis	Dry cough, nasal congestion, fatigue, myalgia, arthralgia, diarrhea, ageusia, anosmia	Yes	No	No	NA	https://doi.org/10.1111/jdv.16474

F, Female; *M*, male; *NA*, not available.
*References supporting this table are available from the corresponding author upon request.

Table II. Summary of possible mucocutaneous adverse effects reported for proposed COVID-19 treatments*

Treatment	Mucocutaneous adverse effects
Chloroquine/hydroxychloroquine†	• Common: itching, hair loss • Less common: morbilliform rash, erythroderma, exfoliative dermatitis, urticaria, eczematous eruption, erythema annulare centrifugum, photosensitivity • Rare: acute generalized exanthematous pustulosis
Azithromycin†	• Rare: morbilliform rash
Lopinavir/ritonavir	• Common: morbilliform rash • Rare: acute generalized exanthematous pustulosis, hair loss
Corticosteroids	• Common: skin atrophy, acneiform eruption, telangiectasia, petechiae, ecchymosis, striae, hirsutism
Tocilizumab	• Less common: anaphylaxis • Rare: morbilliform rash, erythroderma, leukocytoclastic vasculitis
Convalescent plasma	• Less common: morbilliform rash, itching, evanescent red spot

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†Combination treatment increases the risk of QT prolongation.

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