

Cutaneous Manifestations of COVID-19

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PRACTICE POINTS

- Coronavirus disease 2019 (COVID-19) is a worldwide pandemic that affects multiple organ systems via a pathogenesis that is still being elucidated.
- Understanding the various cutaneous manifestations of COVID-19 will aid in early detection and proper treatment, thus increasing patient satisfaction and outcomes.

Patients with coronavirus disease 2019 (COVID-19) present with multisystem signs and symptoms, including dermatologic manifestations. The recent literature has revealed that dermatologic manifestations of COVID-19 often are early onset and provide helpful cues to a timely diagnosis. We compiled the relevant emerging literature regarding the dermatologic manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) so that physicians can be aware of the various clinical cutaneous presentations in this time of high incidence of COVID-19.

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The pathogenesis of coronavirus disease 2019 (COVID-19), the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is not yet completely understood. Thus far, it is known to affect multiple organ systems, including gastrointestinal, neurological, and cardiovascular, with typical clinical symptoms of COVID-19

including fever, cough, myalgia, headache, anosmia, and diarrhea.¹ This multiorgan attack may be secondary to an exaggerated inflammatory reaction with vasculopathy and possibly a hypercoagulable state. Skin manifestations also are prevalent in COVID-19, and they often result in polymorphous presentations.² This article aims to summarize cutaneous clinical signs of COVID-19 so that dermatologists can promptly identify and manage COVID-19 and prevent its spread.

Methods

A PubMed search of articles indexed for MEDLINE was conducted on June 30, 2020. The literature included observational studies, case reports, and literature reviews from January 1, 2020, to June 30, 2020. Search terms included *COVID-19*, *SARS-CoV-2*, and *coronavirus* used in combination with *cutaneous*, *skin*, and *dermatology*. All of the resulting articles were then reviewed for relevance to the cutaneous manifestations of COVID-19. Only confirmed cases of COVID-19 infection were included in this review; suspected unconfirmed cases were excluded. Further exclusion criteria included articles that discussed dermatology in the time of COVID-19 that did not explicitly address its cutaneous manifestations. The remaining literature was evaluated to provide dermatologists and patients with a concise resource for the cutaneous signs and symptoms of COVID-19. Data extracted from the literature included geographic region, number of patients with skin findings, status of COVID-19 infection and timeline, and cutaneous signs. If a cutaneous sign was not given a clear diagnosis in the literature, the senior authors

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The eTable is available in the Appendix online at www.mdedge.com/dermatology.

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(A.L. and J.J.) assigned it to its most similar classification to aid in ease of understanding and clarity for the readers.

Results

A search of the key terms resulted in 75 articles published in the specified date range. After excluding overtly irrelevant articles and dermatologic conditions in the time of COVID-19 without confirmed SARS-CoV-2 infection, 25 articles ultimately met inclusion criteria. Relevant references from the articles also were explored for cutaneous dermatologic manifestations of COVID-19. Cutaneous manifestations that were repeatedly reported included chilblainlike lesions; acrocyanosis; urticaria; pityriasis rosea-like cutaneous eruption; erythema multiforme-like, vesiculopapular, and morbilliform eruptions; petechiae; livedo reticularis; and purpuric livedo reticularis (dermatologists may label this stellate purpura). Fewer but nonetheless notable cases of androgenic alopecia, periorbital dyschromia, and herpes zoster exacerbations also were documented. The Table summarizes the reported integumentary findings. The eTable groups the common findings and describes patient age, time to onset of cutaneous sign, and any prognostic significance as seen in the literature.

Chilblainlike Lesions and Acrocyanosis—Chilblainlike lesions are edematous eruptions of the fingers and toes. They usually do not scar and are described as erythematous to violaceous papules and macules with possible bullae on the digits. Skin biopsies demonstrate a histopathologic pattern of vacuolar interface dermatitis with necrotic keratinocytes and a thickened basement membrane. Lymphocytic infiltrate presents in a perieccrine distribution, occasionally with plasma cells. The dermatopathologic findings mimic those of chilblain lupus but lack dermal edema.³

These eruptions have been reported in cases of COVID-19 that more frequently affect children and young adults. They usually resolve over the course of viral infection, averaging within 14 days. Chilblainlike eruptions often are associated with pruritus or pain. They commonly are asymmetrical and appear more often on the toes than the fingers.⁴ In cases of COVID-19 that lack systemic symptoms, chilblainlike lesions have been seen on the dorsal fingers as the first presenting sign of infection.⁵

Acral erythema and chilblainlike lesions frequently have been associated with milder infection. Another positive prognostic indicator is the manifestation of these signs in younger individuals.³

Integumentary Manifestations of Coronavirus Disease 2019

Integumentary manifestations	Description
Chilblainlike lesions	Erythematous to violaceous papules and macules with or without blistering on the acral areas
Acrocyanosis	Bluish discoloration of the hands or feet
Urticaria	Blanching erythematous papules and plaques
Pityriasis rosea-like cutaneous eruption	Scaly red patches in a tree distribution and a herald patch (a larger oval patch)
Morbilliform eruption	Rose-colored macules and papules
Vesiculopapular eruption	Well-demarcated vesicles, bullae, and erythematous papules
Petechiae	Red to violaceous, nonblanching, pinpoint hemorrhages
Livedo reticularis	Blanching, purplish, reticulated vascular pattern
Stellate purpura	Nonblanching, reticulated, necrosing vascular pattern
Erythema multiforme-like eruption	Erythematous targetoid lesions, mainly on the distal extremities
Androgenic alopecia	Hair loss around the temples, hairline, and vertex scalp
Mottled skin	Blotchy, erythematous to violaceous, irregular streaks and patches of the skin, more commonly on the lower extremities
Periorbital dyschromia	Hyperpigmentation and distortion of skin color surrounding the orbit
Herpes zoster	Erythematous grouped vesicles with hemorrhagic crust in a dermatomal distribution

Morbilloform Exanthem—The morbilliform exanthem associated with COVID-19 also typically presents in patients with milder disease. It often affects the buttocks, lower abdomen, and thighs, but spares the palms, soles, and mucosae.⁴ This skin sign, which may start out as a generalized morbilliform exanthem, has been seen to morph into macular hemorrhagic purpura on the legs. These cutaneous lesions typically spontaneously resolve.⁸

In a case report by Najarian,⁶ a morbilliform exanthem was seen on the legs, arms, and trunk of a patient who was otherwise asymptomatic but tested positive for COVID-19. The morbilliform exanthem then became confluent on the trunk. Notably, the patient reported pain of the hands and feet.⁶

Another case report described a patient with edematous annular plaques on the palms, neck, and upper extremities who presented solely with fever.⁷ The biopsy specimen was nonspecific but indicated a viral exanthem. Histopathology showed perivascular lymphocytic infiltrate, dermal edema and vacuoles, spongiosis, dyskeratotic basilar keratinocytes, and few neutrophils without eosinophils.⁷

Eczematous Eruption—A confluent eczematous eruption in the flexural areas, the antecubital fossae, and axillary folds has been found in COVID-19 patients.^{21,22} An elderly patient with severe COVID-19 developed a squamous erythematous periumbilical patch 1 day after hospital admission. The cutaneous eruption rapidly progressed to digitate scaly plaques on the trunk, thighs, and flank. A biopsy specimen showed epidermal spongiosis, vesicles containing lymphocytes, and Langerhans cells. The upper dermis demonstrated a lymphohistiocytic infiltrate.²³

Pityriasis Rosea-Like Eruption—In Iran, a COVID-19-infected patient developed an erythematous papulosquamous eruption with a herald patch and trailing scales 3 days after viral symptoms, resembling that of pityriasis rosea.²⁴ Nests of Langerhans cells within the epidermis are seen in many viral exanthems, including cases of COVID-19 and pityriasis rosea.²⁵

Urticaria—According to a number of case reports, urticarial lesions have been the first presenting sign of COVID-19 infection, most resolving with antihistamines.^{10,11} Some patients with more severe symptoms have had widespread urticaria. An urticarial exanthem appearing on the bilateral thighs and buttocks may be the initial sign of infection.^{12,15} Pruritic erythematous plaques over the face and acral areas is another initial sign. Interestingly, pediatric patients have reported non-pruritic urticaria.⁹

Urticaria also has been seen as a late dermatologic sign of viral infection. After battling relentless viral infection for 1 month, a pruritic, confluent, ill-defined eruption appeared along a patient's trunk, back, and proximal extremities. Histopathologic examination concluded a perivascular lymphocytic infiltrate and dilated vessels in the dermis. The urticaria resolved a week later, and the patient's nasopharyngeal swab finally came back negative.¹³

Vesiculopapular Eruption—Vesicles mimicking those of chickenpox have been reported. A study of 375 confirmed cases of COVID-19 by Galván Casas et al¹² showed a 9% incidence of this vesicular eruption. A study by Sachdeva et al⁸ revealed vesicular eruptions in 25 of 72 patients. Pruritic papules and vesicles may resemble Grover disease. This cutaneous sign may be seen in the submammary folds, on the hips, or diffusely over the body.

Erythema Multiforme-Like Eruption—Targetoid lesions similar to those of erythema multiforme erupted in 2 of 27 patients with mild COVID-19 infection in a review by Wollina et al.⁴ In a study of 4 patients with erythema multiforme-like eruptions after COVID-19 symptoms resolved, 3 had palatal petechiae. Two of 4 patients had pseudovesicles in the center of the erythematous targetoid patches.²⁶ Targetoid lesions on the extremities have been reported in pediatric patients with COVID-19 infections. These patients often present without any typical viral symptoms but rather just a febrile exanthem or exanthem alone. Thus, to minimize spread of the virus, it is vital to recognize COVID-19 infection early in patients with a viral exanthem during the time of high COVID-19 incidence.⁴

Livedo Reticularis—In the United States, a case series reported 2 patients with transient livedo reticularis throughout the course of COVID-19 infection. The cutaneous eruption resembled erythema ab igne, but there was no history of exposure to heat.¹⁶

Stellate Purpura—In severe COVID-19 infection, a reticulated nonblanching purpura on the buttocks has been reported to demonstrate pauci-inflammatory vascular thrombosis, complement membrane attack complex deposition, and endothelial injury on dermatopathology. Stellate purpura on palmoplantar surfaces also has shown arterial thrombosis in the deep dermis due to complement deposition.¹⁷

Petechiae and Purpura—A morbilliform exanthem may develop into significant petechiae in the popliteal fossae, buttocks, and thighs. A punch biopsy specimen demonstrates a perivascular lymphocytic infiltrate with erythrocyte extravasation and papillary dermal edema with dyskeratotic cells.¹⁸ Purpura of the lower extremities may develop, with histopathology showing fibrinoid necrosis of small vessel walls, neutrophilic infiltrate with karyorrhexis, and granular complement deposition.¹⁹

In Thailand, a patient was misdiagnosed with dengue after presenting with petechiae and low platelet count.²⁰ Further progression of the viral illness resulted in respiratory symptoms. Subsequently, the patient tested positive for COVID-19. This case demonstrates that cutaneous signs of many sorts may be the first presenting signs of COVID-19, even prior to febrile symptoms.²⁰

Androgenic Alopecia—Studies have shown that androgens are related in the pathogenesis of COVID-19. Coronavirus disease 2019 uses a cellular co-receptor, TMPRSS2, which is androgen regulated.²⁷ In a study of 41 males with COVID-19, 29 had androgenic alopecia.

However, this is only a correlation, and causation cannot be concluded here. It cannot be determined from this study whether androgenic alopecia is a risk factor, result of COVID-19, or confounder.²⁸

Exaggerated Herpes Zoster—Shors²⁹ reported a herpes zoster eruption in a patient who had symptoms of COVID-19 for 1 week. Further testing confirmed COVID-19 infection, and despite prompt treatment with valacyclovir, the eruption was slow to resolve. The patient then experienced severe postherpetic neuralgia for more than 4 weeks, even with treatment with gabapentin and lidocaine. It is hypothesized that because of the major inflammatory response caused by COVID-19, an exaggerated inflammation occurred in the dorsal root ganglion, resulting in relentless herpes zoster infection.²⁹

Mottled Skin—Born at term, a 15-day-old neonate presented with sepsis and mottling of the skin. The patient did not have any typical COVID-19 symptoms, such as diarrhea or cough, but tested positive for COVID-19.³⁰

Periorbital Dyschromia—Kalner and Vergilis³¹ reported 2 cases of periorbital dyschromia prior to any other COVID-19 infection symptoms. The discoloration improved with resolution of ensuing viral symptoms.³¹

Comment

Many dermatologic signs of COVID-19 have been identified. Their individual frequency and association with viral severity will become more apparent as more cases are reported. So far during this pandemic, common dermatologic manifestations have been polymorphic in clinical presentation.

Onset of Skin Manifestations—The timeline of skin signs and COVID-19 symptoms varies from the first reported sign to weeks after symptom resolution. In the Region of Murcia, Spain, Pérez-Suárez et al¹⁴ collected data on cutaneous signs of patients with COVID-19. Of the patients studied, 9 had tests confirming COVID-19 infection. Truncal urticaria, sacral ulcers, acrocyanosis, and erythema multiforme were all reported in patients more than 2 weeks after symptom onset. One case of tinea infection also was reported 4 days after fever and respiratory symptoms began.¹⁴

Presentation—Coronavirus disease 2019 has affected the skin of both the central thorax and peripheral locations. In a study of 72 patients with cutaneous signs of COVID-19 by Sachdeva et al,⁸ a truncal distribution was most common, but 14 patients reported acral site involvement. Sachdeva et al⁸ reported urticarial reactions in 7 of 72 patients with cutaneous signs. A painful acral cyanosis was seen in 11 of 72 patients. Livedo reticularis presented in 2 patients, and only 1 patient had petechiae. Cutaneous signs were the first indicators of viral infection in 9 of 72 patients; 52 patients presented with respiratory symptoms first. All of the reported cutaneous signs spontaneously resolved within 10 days.⁸

Recalcati³² reviewed 88 patients with COVID-19, and 18 had cutaneous signs at initial onset of viral infection or during hospitalization. The most common integumentary sign reported in this study was erythema, followed by diffuse urticaria, and then a vesicular eruption resembling varicella infection.³²

Some less common phenomena have been identified in patients with COVID-19, including androgenic alopecia, exaggerated herpes zoster and postherpetic neuralgia, mottled skin, and periorbital dyschromia. Being aware of these complications may help in early treatment, diagnosis, and even prevention of viral spread.

Pathogenesis of Skin Manifestations—Few breakthroughs have been made in understanding the pathogenesis of skin manifestations of SARS-CoV-2. Acral ischemia may be a manifestation of COVID-19's association with hypercoagulation. Increasing fibrinogen and prothrombin times lead to disseminated intravascular coagulation and microthrombi. These tiny blood clots then lodge in blood vessels and cause acral cyanosis and subsequent gangrene.² The proposed mechanism behind this clinical manifestation in younger populations is the hypercoagulable state that COVID-19 creates. Conversely, acral erythema and chilblainlike lesions in older patients are thought to be from acral ischemia as a response to insufficient type 1 interferons. This pathophysiologic mechanism is indicative of a worse prognosis due to the large role that type 1 interferons play in antiviral responses. Coronavirus disease 2019 similarly triggers type 1 interferons; thus, their efficacy positively correlates with good disease prognosis.³

Similarly, the pathogenesis for livedo reticularis in patients with COVID-19 can only be hypothesized. Infected patients are in a hypercoagulable state, and in these cases, it was uncertain whether this was due to a disseminated intravascular coagulation, cold agglutinins, cryofibrinogens, or lupus anticoagulant.¹⁶

Nonetheless, it can be difficult to separate the primary event between vasculopathy or vasculitis in larger vessel pathology specimens. Some of the studies' pathology reports discuss a granulocytic infiltrate and red blood cell extravasation, which represent small vessel vasculitis. However, the gangrene and necrotic livedo represent vasculopathy events. A final conclusion about the pathogenesis cannot be made without further clinical and histopathologic evaluation.

Histopathology—Biopsy specimens of reported morbiliform eruptions have demonstrated thrombosed vessels with evidence of necrosis and granulocytic infiltrate.²⁵ Another biopsy specimen of a widespread erythematous exanthem demonstrated extravasated red blood cells and vessel wall damage similar to thrombophilic arteritis. Other reports of histopathology showed necrotic keratinocytes and lymphocytic satellitosis at the dermoepidermal junction, resembling Grover disease. These cases demonstrating necrosis suggest a strong cytokine reaction from the virus.²⁵ A concern with these biopsy

findings is that morbilliform eruptions generally show dilated vessels with lymphocytes, and these biopsy findings are consistent with a cutaneous small vessel vasculitis. Additionally, histopathologic evaluation of purpuric eruptions has shown erythrocyte extravasation and granulocytic infiltrate indicative of a cutaneous small vessel vasculitis.

Although most reported cases of cutaneous signs of COVID-19 do not have histopathologic reports, Yao et al³³ conducted a dermatopathologic study that investigated the tissue in deceased patients who had COVID-19. This pathology showed hyaline thrombi within the small vessels of the skin, likely leading to the painful acral ischemia. Similarly, Yao et al³³ reported autopsies finding hyaline thrombi within the small vessels of the lungs. More research should be done to explore this pathogenesis as part of prognostic factors and virulence.

Conclusion

Cutaneous signs may be the first reported symptom of COVID-19 infection, and dermatologists should be prepared to identify them. This review may be used as a guide for physicians to quickly identify potential infection as well as further understand the pathogenesis related to COVID-19. Future research is necessary to determine the dermatologic pathogenesis, infectivity, and prevalence of cutaneous manifestations of COVID-19. It also will be important to explore if vasculopathic lesions predict more severe multisystem disease.

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APPENDIX

eTABLE. Cutaneous Signs of Coronavirus Disease 2019, Age Group, Timeframe, and Possible Prognostic Significance

Cutaneous sign	Patient age group	Timing of onset in relation to infection symptoms	Prognostic significance
Chilblainlike lesions	Children and young adults ^a	Up to 10 d prior to other symptoms of infection, at the time of infection, or with no other symptoms ³⁻⁵	Usually resolve with viral infection resolution or are associated with asymptomatic infection ^{4,5}
Morbilliform exanthem	Adults ^b	At symptom onset or with no other symptoms ^{6,7}	Seen in mild or even asymptomatic infection, typically spontaneously resolves ⁶⁻⁸
Urticaria	Children and elderly ^c	Ranging from no other symptoms, ⁹ at symptom onset, ⁹⁻¹¹ or up to 1 mo after infection onset ^{9,12-14}	Seen in otherwise asymptomatic patients ^{12,15} but also in more severe infection ^{9,12,13} ; usually clears with viral resolution ^{9,13}
Vesiculopapular eruption	Adults and elderly ^d	Ranging from 4 d prior to symptoms, at symptom onset, and 2 wk after symptom onset ^{8,12}	Seen in intermediate infection, typically resolves within 1 wk after infection resolution ^{8,12}
Petechiae and purpura	Adults and elderly ^e	Ranging from 3–20 d after symptom onset ¹⁶⁻¹⁹ or with no other symptoms of infection ²⁰	Seen in more severe infection ¹⁶⁻¹⁹

^aReported as a 23-year-old,³ a review with mean age of 14 years old,⁴ and a case series of 2 patients who were 27 and 35 years of age.⁵

^bReported as a review with unspecified age for this cutaneous manifestation,⁸ as well as in a 58-year-old⁶ and a 39-year-old.⁷

^cReported as a 71-year-old,¹⁰ 27-year-old,¹¹ review with mean age of 48.7 years old,¹² 61-year-old,¹⁵ case series of 6-year-old and 2-month-old,⁹ and 67-year-old.¹³

^dReported as 71-, 77-, and 72-year-olds⁸ and a review with mean age of 45.6 years.¹²

^eReported as a case series of 66- and 40-year-olds,¹⁷ a 48-year-old,¹⁸ a 71-year-old,¹⁹ and an adult of unspecified age.²⁰