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Clinical Patterns and Morphology of COVID-19 Dermatology



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KEYWORDS

• COVID-19 • SARS-CoV-2 • Dermatology • Morphology

KEY POINTS

- Numerous skin manifestations associated with COVID-19 have been reported. Dermatologists should be aware of these cutaneous manifestations, which may help with diagnosis, management, and prognosis.
- The most commonly reported cutaneous manifestations associated with COVID-19 infection include pernio (chilblain)-like acral lesions, morbilliform (exanthematous) rash, urticaria, vesicular (varicella-like) eruptions, and vaso-occlusive lesions (livedo racemosa, retiform purpura).
- It is important to consider COVID-19 on the differential diagnosis for these disease entities in the proper clinical context, as dermatologic findings of COVID-19 can be a presenting sign in an otherwise minimally or asymptomatic individual.

INTRODUCTION

In December 2019, unexplained pneumonia cases were reported in Wuhan, China. The new pathogen, named SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), was isolated from samples of the respiratory tract of infected patients, and the resulting disease was called COVID-19 (coronavirus disease 2019). The virus traveled rapidly throughout the globe and was characterized as a pandemic by the World Health Organization on March 11, 2020.

It was soon recognized that COVID-19 patients were experiencing myriad clinical manifestations involving multiple organ systems (including the central nervous, gastrointestinal, and cardiovascular systems), as well as viral illness-induced coagulopathy.^{1–4} Initial case series rarely documented skin changes, possibly due to the lack of dermatologists caring for patients with COVID-19 infection as well as the inability to perform complete skin examinations in critically ill patients. Dermatologists also experienced significant

challenges collecting samples and taking clinical images while maintaining strict infection prevention techniques, particularly with a widespread limited supply of personal protective equipment.⁵ In an early cohort study of 1099 patients with laboratory-confirmed COVID-19, only 2 patients were noted to have “skin rash.”⁶

Shortly thereafter, small cohorts of patients were being reported to have cutaneous findings possibly associated with COVID-19 infection.^{7,8} The reported findings ranged from those more commonly seen in viral infections, such as morbilliform eruptions and urticaria, to more unique, such as pernio and varicelliform eruptions. A large case series describing patterns of skin manifestations among 375 patients highlighted 5 predominant morphologic patterns: maculopapular, urticarial, pernio-like, vesicular, and livedoid.⁹ This series also provided for the first time, a temporal relationship between cutaneous lesions, systemic symptoms, as well as severity of disease. As COVID-19 testing was initially only available to

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those with severe disease, the true incidence of cutaneous manifestations with COVID-19 infection is not yet known. The pandemic has encouraged broad collaboration among physicians and scientists around the world,¹⁰ facilitated by multiple registries, which are helping us increase our understanding of dermatologic manifestations in patients with COVID-19.^{11,12}

Virology/Immunology

SARS-CoV-2 is a single-stranded RNA virus composed of 16 nonstructural proteins, each of which plays a specific role in replication.¹³ SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors, which is known to be found in the lungs (surfactant producing alveolar type 2 cells) as well as the cardiovascular, gastrointestinal, pulmonary, and renal systems.¹⁴ Expression of ACE2 in the skin is highest in keratinocytes, followed by sweat glands. The widespread expression of ACE2 in the skin is just one of the potential reasons for cutaneous manifestations seen with COVID-19 infection.^{15,16}

Pernio (chilblain)-Like Acral Lesions

Since the outbreak of SARS-CoV-2, reports of pernio-like acral lesions have rapidly accumulated. Pernio (chilblains) is an idiopathic cold-sensitive inflammatory disorder that manifests as pink to violaceous macules, papules, plaques, or nodules at sites of cold exposure, commonly on the fingers or toes.¹⁷ Chilblains may be idiopathic or may be associated with autoimmune conditions (ie, chilblains lupus), hematologic malignancies, genetic mutations, and less commonly infections, such as Epstein-Barr virus (EBV).¹⁸ When EBV-associated, cold agglutinins are thought to play a role in pathogenesis.¹⁸ Skin findings may be accompanied by pruritus, pain, burning, and sometimes blistering or ulceration. When making a diagnosis of chilblains, it is important to rule out Parvovirus B19 infection, which can present with acral purpuric lesions.

The first report of pernio-like lesions thought to be associated with COVID-19 was of an Italian adolescent (with family members suspected of having COVID-19 infection) who developed purpuric lesions on the feet before developing systemic symptoms such as fever and myalgias.¹⁹ Reports of young adults with skin lesions on hands and feet identical to chilblains began appearing, seemingly later in the course of their infection.⁹ Analysis of Google Trends data, which illustrates popularity of search trends over a period in a particular location, demonstrated that there were sharp increases in search terms including chilblains,

fingers, and toes in early 2020.^{20,21} As this phenomenon became better known and circulated on social media, it was colloquialized as “COVID-toes,” although the precise relationship with SARS-CoV-2 continues to be elucidated. The association was first suspected for multiple reasons: there was a spike in cases during the pandemic, at an atypical time of year for symptoms to occur (spring), in temperate areas, and in patients typically at low risk (ie, no known comorbid conditions associated with chilblains such as autoimmunity,²² connective tissue disease such as lupus erythematosus, Raynaud phenomenon/syndrome, or a history of chilblains).

Before the pandemic, pernio was uncommon; one case series reported an average of 9 to 10 diagnoses per year across an entire tertiary academic center.¹⁸ Since the onset of the pandemic, studies from around the world have reported numerous individuals with pernio-like lesions thought to be associated with COVID-19 infection. In a French retrospective study on skin manifestations during the early COVID-19 outbreak, pernio-like lesions were noted in 38.3% (106 of 277) of dermatologic outpatients.²³ More recently, an international registry of COVID-19 dermatologic manifestations has recorded 619 cases of pernio in patients with suspected or confirmed COVID-19 infection.²⁴ Patients with pernio-like lesions are noted to present with pruritus and pain of their toes (less often fingers or heels), which progresses to pink-red papules or plaques and then to violaceous purpuric lesions.²⁵ Rarely, pernio-like lesions have been reported in other acral sites, such as on the ear.²⁶ In addition to pernio-like lesions, variations in morphologies have been reported, including erythema multiforme (EM)-like (round, maculopapular, or targetoid lesions), punctiform purpuric lesions, diffuse vascular erythema, and edema of the dorsum/sole of foot or palms.²⁷ Patients with COVID-19 who develop pernio have relatively mild courses; with 2% to 16% of patients with pernio-like lesions being hospitalized.^{9,28-32} This can be compared to other dermatologic manifestations associated with more severe disease such as retiform purpura, where 100% of patients were hospitalized, with 82% of patients developing acute respiratory distress syndrome.²⁸ Pernio-like acral lesions should be recognized as distinct from acroischemic lesions. The two terms were initially used synonymously, but acroischemic lesions are now known to represent a separate manifestation seen among critically ill patients with hypercoagulopathy and/or disseminated intravascular coagulation.⁸

Histopathology of pernio-like lesions is similar to that of idiopathic or systemic disease-associated chilblains. Pathology frequently contains vascular changes, dermal edema, and a superficial and deep perivascular lymphocytic infiltrate. In select reports, immunohistochemistry has confirmed vasculitis of dermal vessels, deposition of immunoglobulins or complement on dermal vessels, and platelet aggregation.^{22,31} When histologic findings of pernio-like lesions in multiple reports were reviewed, it appears that these lesions are primarily inflammatory, nonischemic, and not reflective of systemic coagulopathy, unlike retiform purpura or acral ischemia.²⁸ Furthermore, the microthrombi seen in a small subset of patients with chilblains are likely secondary to the inflammation and clinically correlate with a bullous or necrotic phenotype.³³

In a study of dermoscopy features of COVID-19-related chilblains in children and adolescents, dermoscopic findings were found to correlate with clinical and histopathologic findings of COVID-19-related chilblains. For example, the background color noted on dermoscopy is an indicator of vascular macules, hemosiderin, and inflammatory cells in the dermis; gray areas may be indicative of an ischemic phenomenon, and globules likely representing damaged vessels with extravasated red cells. The specificity of these findings, however, is unclear as there is no dermoscopic study of primary chilblains or chilblains secondary to other causes.^{34,35}

Overall, pernio-like lesions are typically seen in patients with relatively mild COVID-19 disease courses and resolve within 2 to 8 weeks (median 12 days in laboratory-confirmed cases).^{32,36,37} However, persistent and recurrent lesions have been reported. Recent data illustrate a subset of patients with “long COVID” in the skin who had dermatologic signs of COVID-19 that persisted longer than 60 days, including 7 of 103 cases of pernio.³⁷ Recurrent pernio-like lesions in the absence of reinfection have also been noted, with patients who complained of pernio in the fall experiencing an absence of symptoms in the summer, despite surges of COVID-19 infections in the warmer months.²⁴ Of note, pernio lesions in type I interferonopathies are also known to flare with cold exposure.³⁸

There are increasing number of reports suggesting a direct association between pernio-like lesions and SARS-CoV-2. Positive anti-SARS-CoV-2 immunostaining and viral spike protein have been demonstrated in lesional skin biopsy specimens (endothelial cells and eccrine glands) in adult and pediatric patients with pernio-like lesions.^{39–41} However, owing to lack of specificity,

some authors have suggested that these findings be interpreted with caution.^{42–44}

The pathogenesis of pernio-like lesions is not well understood but is thought to be predominantly an inflammatory process similar to idiopathic and autoimmune-related chilblains. The striking similarity of pernio-like lesions to those observed in type I interferonopathies (ie, Aicardi-Goutieres syndrome and STING-associated vasculopathy) has raised the suspicion of the important role of interferon (IFN) despite the absence of other manifestations of interferonopathies in patients with COVID-19 infection.^{45–47} One group demonstrated induction of the type I IFN pathway in lesional sections of COVID-19-associated chilblain-like lesions.⁴⁸ Type I interferon is known to have an important role in the pathogenesis of lupus erythematosus.^{49,50} Furthermore, interferons are also thought to induce microangiopathic changes contributing to the development of chilblains lupus.^{46,47}

As mounting evidence suggests a direct association with SARS-CoV-2, pernio-like lesions are currently believed to represent a postviral or late-onset finding after COVID-19 infection, especially in those who can mount a robust IFN response. In a report by Freeman and colleagues, 80 of 318 cases developed pernio-like lesions after the onset of other symptoms of COVID-19 infection; a similar finding has been noted in at least one other study.^{9,32} Conversely, pernio-like lesions have also been reported to occur concurrently with RT-PCR test positivity.^{32,51} Negative nasopharyngeal reverse-transcription polymerase chain reaction (RT-PCR) or anti-SARS-CoV-2 serologies in many patients^{52–58} created uncertainty early in the pandemic regarding the precise relationship.^{39,54,57–59} Indeed, some patients who were RT-PCR negative after developing pernio, were later found to have positive COVID-19 antibodies (immunoglobulin M, G, or A).^{24,26,32,60,61}

What was initially surprising, however, was that serologic testing for IgM or IgG antibodies was often negative. There is increased understanding of this mechanism:

- I. Early in the pandemic, interpretation of RT-PCR/antibody results in patients with skin rash and probable COVID-19 was difficult due to lack of understanding of timing and antibody kinetics. Much of the available antibody data were drawn from patients with more severe illness as widespread testing was not available. Many patients with pernio-like lesions were undergoing serologic evaluation for SARS-CoV-2 antibodies early in the disease course. In one study,

patients had antibody testing between 3 and 30 days after pernio developed, with most evaluated less than 15 days after pernio onset.⁵⁷ It is now appreciated that delayed antibody development after infection with SARS-CoV-2 is common.⁶² In one early report, positive antibodies were detected a median of 30 days from disease onset, beyond the typical 14- to 21-day testing window.⁶³

- II. Population level antibody testing from the past year has revealed that there is a relationship between disease severity and the level of SARS-CoV-2 antibodies. In one particular hospital, for both IgG and IgA isotypes, patients with moderate/severe infection had significantly higher antibody titers within the first 1.5 months after diagnosis compared to those with milder disease.⁶⁴ As previously discussed, it is now well-established that those with COVID-19 who develop chilblains have relatively mild clinical courses and may not mount a marked antibody response, similar to others with minimal symptoms of infection.⁶⁰ Despite a more muted antibody response, data suggest that patients with milder SARS-CoV-2 infection are able to elicit *in vitro* neutralizing antibodies (preventing the virus from entering epithelial cells).⁶⁵ Negative RT-PCR on nasopharyngeal swabs is supportive of the notion that pernio-like lesions are a late symptom of COVID-19.²⁸
- III. Most serologic testing for SARS-CoV-2 currently is against SARS-CoV-2 IgM and IgG. It is appreciated that the host immune response to SARS-CoV-2 infection includes synthesis of several types of virus-specific antibodies including IgM, IgG, and IgA.^{66,67} There are also reports that some patients with pernio-like lesions have positive serology for anti-SARS-CoV-2 IgA.^{55,60} The authors postulated that children with mild or asymptomatic infection may develop an IgA humoral response, rather than IgG. Secretory IgA plays a vital role in host protection of mucosal surfaces by preventing entry and subsequent infection by respiratory viruses including influenza; elevated levels are also associated with improved influenza vaccine efficacy.⁶⁸ With SARS-CoV-2, a pathogen that first interacts with the immune system at mucosal surfaces/lungs due to person-to-person respiratory transmission, a robust IgA response appears before IgG. IgA serum levels reach their peak earlier than IgG (10–14 days)

suggesting that both IgA and IgG are part of the initial humoral immune response. Given that currently widely used commercial antibody tests do not look for IgA, a “negative antibody test” may not truly reflect the absence of prior infection and/or antibody production.

- IV. The kinetics of early interferon production may determine overall COVID-19 disease severity and antibody production. Interferons are early antiviral response proteins that interfere with intracellular viral replication, recruit other cells for antiviral response, and cause “flu-like symptoms” such as fever and muscle pain. It is thought that robust production of interferon-I is associated with early viral control, suppressed antibody response, and mild COVID-19 infection. This may be an additional explanation for why some patients fail serologic detection.⁶⁹ Conversely, patients with severe COVID-19 have notably depressed/absent interferon responses or interferon deficiency that can lead to severe, life-threatening COVID-19 infection.^{70–73} Several authors hypothesize that chilblains, specifically, could be the cutaneous expression of a strong type I interferon response.^{74–77} This could therefore explain the absence of antibodies in patients with chilblains.

There is a correlation between the severity of COVID and the timing of appearance of COVID-antigen-specific CD4 T-cells in circulation. Patients with the early expansion of antigen-specific CD4 T-cells (2 days after symptom onset) seem to have mild COVID and those who have a late response (CD4 appearance >20 days after symptoms) have severe disease, suggesting that an early CD4 T-cell response is important in fighting SARS-CoV-2 infection.⁷⁸ Sekine and colleagues have demonstrated T-cell immunity to SARS-CoV-2 in those with mild COVID-19 infection who were also subsequently seronegative.⁷⁹

Morbilloform Eruptions

Morbilloform (maculopapular) eruptions frequently arise as a result of viral infections or adverse drug reactions, and are the most commonly reported cutaneous manifestation of COVID-19 with a prevalence as high as 47%.^{7,9,23,28,80} Predominantly involving the trunk, the rash has been noted either at disease onset, or more frequently, after hospital discharge, with a reported median duration of 7 days.^{7,37,81} Morbilloform eruptions are associated with intermediate severity of disease.⁸² It is difficult to definitively associate

morbilliform eruptions with SARS-CoV-2 infection as many reported patients may have received concomitant drug therapy for their infection. Although medications given as a part of COVID-19 treatment (ie, ribavirin, IVIG, and antiretroviral drugs) may cause morbilliform eruptions, this manifestation has been noted in patients with no new medications.^{83,84} Taking a detailed history is critical, and it is important to consider COVID-19 testing in patients when the eruption is not better explained by medications or other infections.

Urticarial Eruptions

Urticaria (hives) is a common feature among COVID-19 patients who experienced rashes. Acute urticaria, defined as a self-limited lesion lasting less than 6 weeks, has been reported as a presenting sign of COVID-19 infection, although it can also occur later in the disease course.^{7,9,23,28,45} COVID-associated urticaria has also been reported to present with fever as an early prodromal sign in otherwise asymptomatic individuals.^{85–87} Acute urticaria can be triggered by infections, medications, insect bites/stings, and type I immune reactions. It has been hypothesized that viral IgM/IgG can cross-react with mast cell IgE and cause mast cell degranulation, which could explain urticaria in the setting of COVID-19 infection.⁸⁸ It is important to note that urticaria is also a possible side-effect for numerous medications used to treat COVID-19.⁸⁴ COVID-19-associated urticarial eruptions are reported to last a median of 4 days with a maximum duration of 28 days.³⁷ Although the specificity of urticaria to COVID-19 infection is low, in patients with new onset urticaria developing during the pandemic, one should consider evaluation for COVID-19 infection with RT-PCR and serologic studies.

Vesicular Eruptions

Vesicles are fluid-filled collections in the epidermis less than $\frac{1}{2}$ cm in diameter. Vesicles can be caused by a variety of viral infections including varicella-zoster, herpes simplex, echovirus, and coxsackievirus infections.⁸⁹ Most patients with COVID-19 presenting with varicella-like exanthem also have general respiratory and general symptoms of COVID-19 infection. One Italian study including 22 patients reported vesicular, varicelliform lesions, which developed on average 3 days after onset of COVID-19 symptoms.⁹⁰ Although more often being reported as developing early after onset of systemic signs of COVID-19 infection (up to 79.2%),⁹¹ 15% of patients in one study developed this rash before other symptoms.⁹ The papulovesicular exanthems noted in

association with COVID-19 infection differ from true varicella infection with their truncal involvement, scattered distribution, and minimal pruritus.⁹⁰ Vesicular lesions are thought to be associated with moderate severity of COVID-19.^{9,91} In the appropriate clinical context, COVID-19 testing (in addition to HSV/VZV PCR) should be performed in a patient presenting with varicelliform cutaneous eruption.

Two morphologies of COVID-associated vesicular eruption have been described: localized, monomorphic lesions typically involving the trunk or back, and a more diffuse polymorphic eruption notable for small papules, vesicles, and pustules of varying sizes.⁹¹ The distribution of lesions involving the trunk and back mimics Grover disease (transient acantholytic dermatosis), a benign condition seen in older Caucasian men with crusted papules and papulovesicles on the trunk and back. COVID-19-associated varicella-like exanthem can share some histologic similarity to Grover disease. In one report of 3 cases, a prominent nonballooning acantholysis with intraepidermal vesicle and eosinophilic dyskeratosis without nuclear atypia was noted, leading to the suggestion that this entity would be better termed “COVID-19-associated acantholytic rash.”⁹² Conversely, in other histologic reports of COVID-19-associated vesicular eruptions, histology was consistent with viral infection, with vacuolar degeneration of the basal layer with multinucleate, hyperchromatic keratinocytes and dyskeratotic cells.^{90,93}

Erythema Multiforme-like Lesions

EM is an acute, typically self-limited hypersensitivity reaction involving the skin and mucous membranes presenting with concentric three-ring targetoid plaques on acral surfaces. It is clinically characterized as presenting with acute onset of concentric (targetoid) plaques. In adults, more than 90% of EM is thought to be triggered by infection, particularly the herpes simplex virus. EM-like eruptions of targetoid lesions with either truncal or acral predominance have been observed in association with SARS-CoV-2 infection in adults and children.^{9,94–97} Children with COVID-19 who develop EM generally have mild respiratory/gastrointestinal symptoms or are otherwise asymptomatic.⁹⁸ In one series, 2 of 4 children with suspected COVID-related EM underwent skin biopsies with positive immunohistochemistry staining of endothelium to SARS-CoV-2 spike protein.⁹⁹ Another study reported 4 hospitalized women with COVID-19 infection who developed pink truncal papules evolving to

targetoid lesions, which resolved in all 4 patients within 2 to 3 weeks.⁹⁴ A 60-year-old woman with fixed urticarial eruption (nonevanescant) underwent skin biopsy, which was notable for slight vacuolar-type interface dermatitis with necrotic keratinocytes and no eosinophils, most consistent with an EM-like pattern, highlighting that not all EM-like lesions present as targets.¹⁰⁰

Pityriasis Rosea-like Eruption

Pityriasis rosea (PR) is a common papulosquamous eruption presenting with ovoid patches and plaques with fine collarettes of scale. In classic cases, a solitary lesion (herald patch) precedes the development of a more diffuse eruption. Lesions are classically formed along skin fold lines on the trunk. PR-like eruptions have been noted to be occurring in greater frequency and in association with SARS-CoV-2 infection.^{101–107} An atypical digitate papulosquamous variant in an elderly patient with COVID-19 infection has also been reported.¹⁰⁸ Although the exact cause of typical PR is unclear, viral etiologies, including human herpesvirus (HHV)-6 and 7 have been favored. Reactivation of HHV-6 and EBV has been demonstrated in one patient with COVID-19 infection and PR.¹⁰⁹ A recent report demonstrated 2 patients with PR-like rash and urticaria-like rash with COVID-19 infection with SARS-CoV-2 spike protein present in the endothelium of dermal blood vessels of affected skin.¹¹⁰ It is unclear if the increased incidence of PR is due to direct viral infection of SARS-CoV-2, reactivation of HHV-6/7, or other factors. Testing for infection is recommended in a patient who presents with this characteristic eruption in the appropriate clinical context.

Pediatric COVID-19

Despite more than 3.85 million testing positive for COVID-19 since the onset of the pandemic, children have been relatively spared from severe COVID-19-related complications, with less frequent infection, less severe respiratory sequelae, and generally a milder course.^{111,112} This milder course is attributed to children having fewer predisposing factors for severe disease (ie, cardiovascular disease, diabetes mellitus), healthy vascular endothelium, strong antiviral innate immunity, and fewer ACE receptors in nasal and lung epithelium, making viral entry and infection more difficult.¹¹³

In children, cutaneous signs of COVID-19 may be the predominant or only clue of infection and, in fact, are not uncommon. Cutaneous lesions of COVID-19 occur in more than 8% of hospitalized

children¹¹⁴ and are the 7th most common extrapulmonary manifestation.¹¹⁵ There are several case reports and case series of various cutaneous eruptions in COVID-positive children. Children with COVID-19 and skin manifestations carry an overall better prognosis than those without.¹¹⁶

Multisystem Inflammatory Syndrome in Children (MIS-C)

Since April 2020, there have been multiple reports worldwide of severe pediatric disease several weeks (median 25 days) after SARS-CoV-2 infection with fevers, multiorgan involvement, and characteristics of Kawasaki disease (KD).^{117–119} This syndrome has been called MIS-C and is thought to be a postviral consequence of COVID-19 infection. There is confirmed laboratory evidence of COVID-19 infection in 99% of cases, antibody testing is positive, and RT-PCR tends to be negative. The US Centers for Disease Control and Prevention (CDC) has developed a case definition of MIS-C (**Table 1**).¹²⁰

MIS-C shares some features of KD and toxic shock syndrome, including fever and skin, mucous membrane, and distal extremity changes. However, it is considered a distinct disease. In contrast to KD, MIS-C is being seen in older children and adolescents (median age 9 years) and non-Hispanic black and Hispanic children, whereas KD more commonly affects children younger than 5 years who are of East Asian descent. In addition, children with MIS-C experience more gastrointestinal symptoms and less than 50% meet formal criteria for KD.^{121,122}

The pathogenesis of MIS-C is thought to be multifactorial, including the robust immune system of children, immune complex activation, and the superantigen activity of SARS-CoV-2 spike protein all leading to cytokine storm and systemic inflammation.^{123–125} MIS-C cases and deaths unfortunately continue to accumulate; although most children with this condition require intensive care, patients with MIS-C carry a good prognosis, with current mortality estimated at 2%.

Although many studies have described cutaneous involvement with MIS-C, the type of rash, distribution, and clinical course needs to be studied further. Greater than 50% of cases of MIS-C are reported to have mucocutaneous changes. Reported mucocutaneous findings include morbilliform, scarlatiniform, urticarial, and reticulated patterns, as well as periorbital edema, malar rash, and reticulated exanthems similar to erythema infectiosum.¹²⁶ In addition, distal extremity changes, oral mucous membrane changes,

Table 1
Case definition for Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19 infection¹²⁰

Criteria	Additional Information	
Age <21 y		
Fever	Fever $\geq 38.0^{\circ}\text{C}$ for ≥ 24 h, or report of subjective fever lasting ≥ 24 h	
Laboratory evidence of inflammation	Including, but not limited to, one or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6, elevated neutrophils, reduced lymphocytes, and low albumin	
Multisystem (≥ 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic)	<i>Organ system</i>	<i>Examples of involvement^{130,131}</i>
	Gastrointestinal	Abdominal pain, diarrhea, nausea, vomiting, abnormal hepatobiliary markers
	Hematologic	Fever, myalgias, lymphadenopathy, fatigue, abnormal blood counts
	Neurologic	Headache, irritability, altered mental status, dizziness
	Dermatologic	Cutaneous eruption, conjunctivitis, edema, mucositis
	Respiratory	Dyspnea, upper respiratory infection-like signs, cough, wheezing, respiratory failure, pulmonary infiltrates
	Cardiovascular	Shock, chest pain, myocarditis, coronary artery dilatation/aneurysm, elevated cardiac enzyme markers
	Renal	Acute kidney injury
No alternative plausible diagnoses; AND		
Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 wk before the onset of symptoms.		

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; LDH, lactic acid dehydrogenase.

conjunctivitis, and purpura are reported.¹²⁷ The molecular mechanisms underlying the relationship between COVID-19 and MIS-C are poorly understood. There are increasing numbers of adults

being reported to have COVID-19–associated MIS-C, characterized by multiorgan dysfunction (particularly cardiac) in the absence of severe respiratory illness.^{128,129}

Vascular Lesions

Petechiae and purpura

Petechiae and purpura (visible hemorrhage into the skin or mucous membranes) are among the less commonly described cutaneous manifestations of COVID-19 infection. The first COVID-19-associated cutaneous manifestation with purpuric features was reported by Joob and colleagues, who described a petechial rash misdiagnosed as dengue in a COVID-19 patient.¹³² Only 3% of patients in a French study of 277 patients had petechial skin lesions.²³ Petechial eruptions can have many etiologies including platelet deficiency or dysfunction, disorders of coagulation, and loss of vascular wall integrity. This morphology is associated with certain viral infections including enterovirus, parvovirus B19, and dengue virus.¹³³ COVID-19-associated petechial and purpuric lesions have been noted on acral surfaces, intertriginous regions, extremities, or diffusely.^{9,23,134–136} When secondary to vasculitis, lesions can progress to form blisters.¹³⁷ Henoch-Schonlein Purpura and IgA vasculitis has been reported to be triggered by SARS-CoV-2 infection.^{138–140}

Livedo reticularis-like lesions

Livedo reticularis (LR) is a transient finding that classically presents with a blue-purple reticulated vascular pattern. LR results from alterations in vascular flow, which results in accumulation of deoxygenated blood in the cutaneous venous plexis. LR has been observed in association with COVID-19 infection.^{141–143} Although cases of LR were grouped with more severe necrosis in a major early study,⁹ more recent reports estimate that this manifestation was present in 3.5% of patients.²⁸

Fixed livedo racemosa, retiform purpura, and necrotic vascular lesions

Vaso-occlusive lesions (livedo racemosa, thrombotic retiform purpura, and acral ischemia) have been noted in elderly, critically ill patients with severe COVID-19 infection.^{9,28,144} These clinical

entities exist at the opposite end of the disease severity spectrum compared to perniosis, which occurs in those with mild or asymptomatic disease. Patients with this clinical finding have been noted to have markedly elevated D-dimer levels and disseminated intravascular coagulation.^{8,144} Skin biopsy of a COVID patient with retiform purpuric patches showed multiple occlusive thrombi in most small vessels of the superficial and mid-dermis.¹⁴⁵ Direct immunofluorescence in this patient was notable for IgM, C3 and C9 deposition within dermal vessel walls.¹⁴⁵ In a subsequent study of a series of COVID patients with retiform purpura, terminal complements C5b-9 and other complement components were found in the microvasculature. This may be suggestive of systemic complement activation and pathophysiology similar to atypical hemolytic uremic syndrome or other microthrombotic syndromes.¹⁴⁴ Pauci-inflammatory purpuric (most often on buttocks) pressure ulcers have also been noted in several critically ill COVID patients with limited mobility, incontinence, and malnutrition.¹⁴⁶ Histopathology of these purpuric pressure ulcers were consistent with pressure necrosis (epidermal necrosis, eccrine gland necrosis); SARS-CoV-2 RNA *in-situ* hybridization of all 4 skin biopsies was negative. The reported patients did not have any laboratory evidence of coagulopathy such as disseminated intravascular coagulation.¹⁴⁶ It is important to recognize that this clinical finding is distinct from the thrombotic vasculopathy noted by Magro and colleagues.¹⁴⁴

In a recent review of the literature, vaso-occlusive lesions were found to be the least commonly reported cutaneous manifestation with COVID-19 infection but may portend a worse prognosis with the highest mortality rate of all COVID-associated cutaneous manifestations (18.2%).^{82,147}

OTHER REPORTED CUTANEOUS MANIFESTATIONS/ASSOCIATIONS

Cutaneous Manifestation	Subtype, if Applicable	Morphology	Additional Clinical Findings
Alopecia	Androgenetic alopecia	Hair loss from the anterior hairline moving posteriorly or thinning at the vertex scalp	Associated with worse clinical outcomes in some studies ^{148,149}
	Telogen effluvium	Diffuse hair shedding 2–3 mo after a stressor ^{150,151}	

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Cutaneous Manifestation	Subtype, if Applicable	Morphology	Additional Clinical Findings
Gianotti-Crosti-like rash		Pruritic erythematous papules and vesicles on elbows, anterior thighs, and bilateral popliteal fossa coalescing into plaques. ¹⁵²	Rash started 18 d after onset of symptoms, 13 d after +COVID test, and 3 d after resolution of all respiratory and systemic symptoms.
SDRIFE-like		Erythematous rash on bilateral axillae and antecubital fossae, which subsequently extended to trunk and inner thighs ^{153,154}	
Grover-disease-like		Red papules and papulovesicles distributed on the trunk ¹⁵⁵ Note: some evidence suggests clinical overlap with vesicular, or "varicella-like" eruptions	
Erythema elevatum diutinum-like		Firm symmetric smooth nodules on extensor surfaces, particularly joints ¹⁵⁶	
Reactive infectious mucocutaneous eruption (formerly known as <i>Mycoplasma</i> -induced rash and mucositis)		Shallow erosions of the vermilion lips, hard palate, periurethral glans penis. ¹⁵⁷	Reported patient with +COVID PCR 1 wk before rash onset, and again positive at rash onset. <i>Mycoplasma</i> PCR negative, IgM negative, IgG positive (consistent with past exposure).
Enanthems (eruptions of the mucous membranes)		83% (5 patients) with petechial enanthem ± macular enanthem ¹⁵⁸	Recorded from a group of 21 patients with COVID-19 and skin rash ranging from papulovesicular, purpuric periflexural, and erythema multiforme-like.
Oral lesions		Aphthous-like, ulcerations, and macules, tongue depapillation, angular cheilitis, ulcers, blisters, white plaques, dark pigmentations. ¹⁵⁹	Etiology postulated to be multifactorial. Hypotheses include direct action of SARS-CoV-2 on oral mucosal cells, coinfection, immunity impairment, or adverse drug reactions ¹⁶⁰
Acute genital ulcers (Lipschütz ulcers)		Necrotic ulcers with raised, sharply demarcated borders of the labia minora with no evidence of "kissing lesions." ¹⁶¹	Single oral aphtha was also observed, with no cutaneous involvement
Transient rash in newborns		Transient "rash" (morphology not described) in babies born to mothers with COVID-19. ¹⁶² Mottling noted in a neonate with sepsis and +COVID-19. ¹⁶³	

Abbreviation: SDRIFE, symmetric drug-related intertriginous and flexural exanthema.

DISCUSSION

As the novel SARS-CoV-2 virus rapidly spread throughout the world, the scientific and medical community has worked with remarkable pace to understand its full clinical effects. Early in the pandemic, scarcity of diagnostic assays limited our ability to confirm infection in patients presenting with an array of cutaneous manifestations. Most young patients presenting with pernio-like lesions had mild clinical courses, which precluded them from having access to COVID-19 testing early in the pandemic when diagnostic resources were limited.

Viral infections are known to produce a variety of clinical findings due not only to their direct action on human cells but also to the host immune response and resulting inflammatory cascade. Further complicating the clinical picture, patients with COVID-19 infections were often treated with a multitude of medications, many of which can be associated with the reported cutaneous manifestations. Now with relative widespread availability of RT-PCR assays and serologic testing, we are beginning to understand the utility and limitations of testing (including timing in relation to a patient's infection course and imperfect sensitivities and specificities of available tests).^{62,164} It is now understood that a negative swab or antibody test at one point in time does not necessarily rule out SARS-CoV-2 as a causative agent.¹⁶⁴ Data derived from a UK COVID Symptoms Study app suggest that those with cutaneous rash are more likely to test positive for SARS-CoV-2 (odds ratio 1.67).¹⁶⁵ Although less prevalent than fever, the authors also found rash to be more specific for COVID-19 infection, which lends support to the diagnostic value of cutaneous manifestations of SARS-CoV-2 infection.¹⁶⁵

The most commonly reported cutaneous manifestations associated with COVID-19 infection include pernio-like, urticarial, morbilliform, and retiform purpura. As previously discussed, identifying cutaneous eruptions and their possible association with SARS-CoV-2 infection can allow for early identification of infection, sometimes even before onset of more classic symptoms such as respiratory distress.⁸² As seen in **Fig. 1**, Jamshidi and colleagues in their systematic review found that vesicular and urticarial eruptions are seen

early relative to other COVID-19 symptoms. Maculopapular, papulosquamous, vascular lesions tend to occur around the time that a patient is symptomatic. Pernio-like lesions occur later in the disease course.⁸² Certain cutaneous morphologies are noted to correlate to severity of illness and overall prognosis. According to a study by Galvan and colleagues, pernio-like, vesicular, urticarial, maculopapular, and livedoid/necrotic lesions were associated with progressively increasing disease severity.⁹ This has been corroborated by another study by Freeman and colleagues, which demonstrated cutaneous manifestations associated with a spectrum of severity, with pernio-like lesions noted in mild disease, vesicular/urticarial/macular erythema/morbilliform eruption in intermediate severity, and retiform purpura in critically ill patients.²⁸ Similarly, pernio-like lesions and morbilliform eruptions are associated with the highest survival rates (98.7% and 98.2%, respectively), whereas vaso-occlusive lesions are associated with the lowest survival rate of 78.9%.¹⁴⁷ It is important to consider SARS-CoV-2 infection in the differential diagnosis of a patient presenting with these lesions (ie, new onset pernio-like lesions, vesicular or morbilliform eruption) in the appropriate clinical context, as cutaneous manifestations may be present in otherwise asymptomatic individuals, or present before developing other symptoms of infection.

The coronavirus pandemic has been found to disproportionately affect people of color in both the United States and the United Kingdom, yet registry data on cutaneous manifestations in this population is lacking.²⁸ A systematic review of literature describing cases of cutaneous manifestations associated with COVID-19 found a significant paucity of reports and photographs of manifestations in skin of color, and no published photos of cutaneous manifestations in Fitzpatrick type V or VI skin.¹⁶⁶ A recent study suggests there are geographic differences in the morphology and prevalence of COVID-19-associated skin manifestations.¹⁴⁷ More work must be done to better understand the true prevalence of skin findings in COVID-19 across all populations and ethnicities.

SUMMARY

The clinical phenotype of COVID-19 includes a broad spectrum of cutaneous manifestations of varying degrees of severity and specificity. Although initially thought to be an infection with primarily internal/systemic manifestations, COVID-19 has taught us that dermatologists play an important role in the treatment of COVID-19 patients, as well as in the broad scientific



Fig. 1. Timing of skin lesions relative to other COVID-19 symptoms.⁸²

collaboration to learn more about the pathophysiology of infection. Widespread availability of COVID-19 tests, as well as improved diagnostic assays, will further assist our understanding of how skin manifestations are related to this viral infection, and parse out potential confounding factors such as concurrent pharmacotherapy or lifestyle changes.

CLINICS CARE POINTS

- Cutaneous manifestations of COVID-19 are generally benign and self-limited. These manifestations have prognostic significance depending on type of skin lesion. Pernio (chilblain)-like acral lesions are generally associated with mild disease; retiform purpura is typically seen in patients on the severe end of the disease severity spectrum.
- Cutaneous manifestations may be present in otherwise asymptomatic individuals, or present before developing other symptoms of infection.
- With increased access to diagnostic testing, we are beginning to understand the utility and limitations of currently available assays.

DISCLOSURE

The authors have nothing to disclose.

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