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Cutaneous Manifestations of COVID-19 in the Inpatient Setting

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KEYWORDS

• COVID-19 • Cutaneous • Inpatient • Vasculopathy • Viral exanthem • Complement • MIS-C

KEY POINTS

- COVID-19 is associated with polymorphic cutaneous manifestations of varying reported prevalence; the diversity of mucocutaneous findings is likely secondary to varying immune responses in response to SARS-CoV-2 infection.
- Cutaneous manifestations of COVID-19 in hospitalized patients can be broadly divided into 2 categories: vasculopathy-related cutaneous lesions and viral exanthem/inflammatory eruptions.
- Among patients hospitalized with COVID-19, patients with vasculopathy-related cutaneous lesions had more severe disease and higher mortality rates.
- Many viral exanthem/inflammatory eruptions are reported more frequently in hospitalized patients; however, these eruptions are associated with less severe COVID-19 than vasculopathy-related findings.
- Prompt recognition of these cutaneous manifestations is paramount to facilitate diagnosis and treatment of COVID-19.

INTRODUCTION

Since December 2019, coronavirus disease 2019 (COVID-19) has spread globally and caused significant morbidity and mortality worldwide. Cutaneous manifestations have been observed in patients with COVID-19 with varying prevalence ranging from 0.2% to 24%.[1–4] However, the true prevalence of cutaneous lesions is difficult to assess. Many studies included patients with both suspected and confirmed cases of COVID-19, and the lack of adequate personal protective equipment, especially at the beginning of the pandemic, may have precluded a thorough skin examination in many patients. A recent publication showed that 35 of 396 patients (11.8%) hospitalized with COVID-19 had dermatologic findings.[5]

Similar to the heterogeneity of systemic symptoms of COVID-19, cutaneous manifestations of COVID-19 are wide-ranging. In addition to varying morphologies, the eruptions affect disparate age groups and exhibit varying time courses; although some portend serious disease, others are associated with milder illness.[6,7] Certain dermatologic conditions are more prevalent in the inpatient compared with the outpatient setting—an important distinction when reviewing the mucocutaneous eruptions associated with COVID-19.[5] It is thought that the varying clinical manifestations are due to patients' differing immune response to the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[8] For example, those who successfully clear SARS-CoV-2 infection due to a robust or even exaggerated type I interferon

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response before humoral immunity occurs are more likely to develop pernio-like lesions ("COVID toes"). Alternatively, those with severe COVID-19 requiring hospitalization are more likely to develop dermatologic manifestations associated with an increased clotting tendency (possibly related to excessive complement activation) resulting in retiform purpura—a condition occurring almost exclusively in the inpatient setting.[9,10]

The pathophysiology of these eruptions is not yet fully elucidated. SARS-CoV-2 can bind to angiotensin-converting enzyme 2 (ACE2) receptors expressed in the subcutaneous fat and epithelial cells,[11] and thus, direct viral invasion has been proposed to contribute to the development of cutaneous manifestations in patients with COVID-19.[9] The roles of a cytokine storm and complement activation have also been implicated.[9,12–14] Recent work has demonstrated the importance of varying type I interferon responses in clinical severity of COVID-19 as well as associated dermatologic findings; higher levels of interferon-alpha, a type I interferon crucial to the early immune response to viral infection, was found to be associated with less severe COVID-19 infection as well as the development of pernio-like lesions.[8]

In this review, we cover common and uncommon skin lesions in patients hospitalized with COVID-19. These skin findings can be broadly divided into 2 categories: vasculopathy-related cutaneous eruptions secondary to systemic dysregulation caused by COVID-19 and eruptions related to virally triggered inflammatory responses similar to skin manifestations from other viral triggers.[14] We review demographic and clinical characteristics associated with each morphology.

VASCULOPATHY-RELATED CUTANEOUS LESIONS

COVID-19 is associated with a hypercoagulable state resulting in arterial and venous thrombosis.[15] In the skin, manifestations of coagulopathy range from transient livedoid reticularis to fixed livedo racemosa, retiform purpura, ulcerations, and necrosis.

Livedo Reticularis

Livedo reticularis is characterized by nonfixed, dusky patches forming complete rings, reflecting the underlying dermal and subcutaneous vasculature, and is caused by partial or intermittent blood flow reduction to the skin.[16] Livedo reticularis was observed in 5.3% of confirmed COVID-19 patients with dermatologic manifestations included in the American Academy of Dermatology's (AAD) COVID-19 registry.[6] However, livedo reticularis was not reported in several other case series that included large numbers of patients[1,3,4] (**Table 1**). Given the scarcity of this morphology, full clinical characterization of livedo reticularis in patients with COVID-19 is not currently possible. However, cases of fluctuating or transient livedo reticularis on the trunk and thigh have been reported.[17,18] Pauci-inflammatory thrombotic vasculopathy was seen in a biopsy of livedo reticularis.[6] Most reported cases were mild, not associated with thromboembolic complications, and resolved without dermatologic treatment; however, one death was reported in a patient with livedo reticularis.[6] The presence of microthromboses or low-grade vascular inflammation and vasodilation resulting from endothelial cell damage due to SARS-CoV-2 infection has been proposed as an etiology.[17,18]

Livedo Racemosa/Retiform Purpura/ Cutaneous Necrosis

Livedo racemosa presents with persistent erythematous to violaceous broken rings that are rarely necrotic or ulcerative, indicating a significant reduction in blood flow to the skin (**Fig. 1**). Livedo racemosa was observed in 2.3% of patients with confirmed COVID-19 in the AAD's COVID-19 registry.[6] Retiform purpura exists on a spectrum with livedo racemosa but is a more severe variant caused by full blockage of cutaneous blood flow leading to persistent purpuric and reticular patches or plaques with frank or impending necrosis and/or ulceration (**Fig. 2**).[16] Retiform purpura was observed in 6.4% of patients with confirmed COVID-19 in the AAD's COVID-19 registry and in 9 of 35 hospitalized COVID-19 patients (25.7%) who developed dermatologic findings.[5,6]

Galvan-Casas et al. observed livedo (type not specified) and necrosis in 6% of patients with suspected and confirmed COVID-19[7] (see **Table 1**). Patients who developed retiform purpura were older, with a median age of 66 years, and sicker, with 91% requiring mechanical ventilation and 82% developing acute respiratory distress syndrome (ARDS).[6,7] Systemic thrombotic events such as deep venous thrombosis or pulmonary embolism occurred in 66% of the patients. With a 10% to 18% mortality rate, livedo racemosa and retiform purpura were among the highest mortality of COVID-19–associated cutaneous manifestations.[6,7]

Livedoid and necrotic skin lesions were also reported in case reports and case series with similarly poor prognosis.[19–22] Patients had varying degrees of alterations in coagulation parameters,

Table 1
Summary of clinical characteristics of COVID-19 patients with cutaneous manifestations

Cutaneous Manifestation	Frequency Among COVID-19 Cutaneous Manifestations (%)	Typical Age Range (years)	Relationship to Noncutaneous Symptoms	Hospitalization (%)[a]	COVID-19 Severity	Mortality Rate (%)[a]	Prominent Histologic Findings
Livedo reticularis[b]	At least 3 reported cases	40's to 60's	After	2/3 reported cases	Mild	0/3 reported cases	Pauci-inflammatory thrombotic vasculopathy
Livedo racemosa/ retiform purpura/livedo and necrosis	2.3/6.4/6	60's	Concurrent or after	86–100	Severe	10–18	Pauci-inflammatory thrombotic vasculopathy
Pressure-associated ulceration and necrosis[b]	At least 25 reported cases	30's to 70's	After	11/25 reported cases	Severe	4/25 reported cases	Thrombotic vasculopathy and pressure necrosis
Multisystem Inflammatory Syndrome in Children	0.3	Children	Concurrent	100	Severe	1.8	Varied
Morbilliform eruptions	21–23	50's to 60's	Concurrent or after	45–80	Moderate	2.6–3.7	Spongiosis, basal cell vacuolation, and perivascular lymphocytic infiltrate
Urticarial eruptions	13.5–26	40's	Concurrent or after	33–44	Mild	1	Lichenoid and vacuolar interface dermatitis

(*continued on next page*)

Table 1
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Cutaneous Manifestation	Frequency Among COVID-19 Cutaneous Manifestations (%)	Typical Age Range (years)	Relationship to Noncutaneous Symptoms	Hospitalization (%)[a]	COVID-19 Severity	Mortality Rate (%)[a]	Prominent Histologic Findings
Vesicular eruptions	7.2	Middle age	Concurrent (though 15% before)	32	Moderate	0	Nonballooning acantholysis leading to intraepidermal unilocular vesicle; epidermal dyskeratosis
Erythema multiforme-like eruptions[b]	3.7	Children – Young Adults	Concurrent or after	NR	Mild	NR	Interface dermatitis with superficial and deep perivascular inflammation
Sweet's syndrome[b]	At least 1 case reported	60's	After	1/1 reported case	Moderate	0/1 reported case	Neutrophilic infiltration with vascular proliferation
Petechiae and purpuric eruptions[b]	At least 14 reported cases	30's to 70's	After	14/14 reported cases	Moderate-severe	0/14 reported cases	NR

Abbreviation: NR, not reported.
[a] Small sample size. Numbers reflect number of cases/reports instead of percentage.
[b] Information based on limited numbers of case reports.

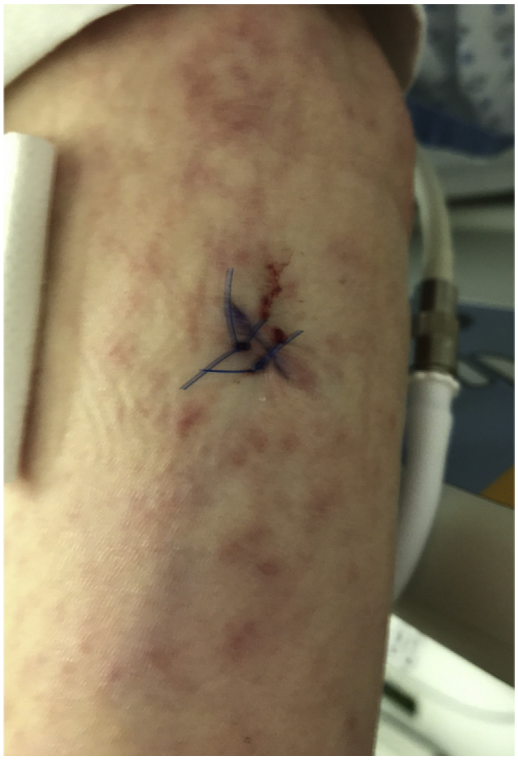

Fig. 1. Livedo racemosa on the arm with biopsy site in a patient with COVID-19 complicated by ARDS. Biopsy revealed pauci-inflammatory thrombotic vasculopathy. From Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. Transl Res. 2020;220:1-13.

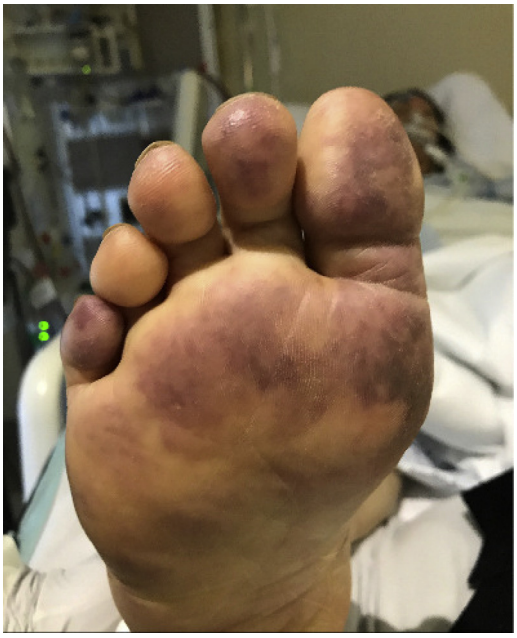

Fig. 2. Early retiform purpura on the right foot in a patient with COVID-19 complicated by ARDS and ischemic stroke. Biopsy revealed pauci-inflammatory thrombotic vasculopathy. From Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. Transl Res. 2020;220:1-13.

most notably elevated d-dimer, and many also had systemic thromboembolic complications. Although disseminated intravascular coagulation (DIC) has been implicated in patients with COVID-19, some patients with livedo racemosa or retiform purpura did not develop classic DIC laboratory parameters.[21,23,24] The presence of antiphospholipid antibodies was variable, as some COVID-19 patients with acro-ischemia were found to have antiphospholipid antibodies though others did not.[19,20,22] Nevertheless, antiphospholipid antibodies can arise transiently in patients with critical illness and infection.[25]

It is rare for these findings to precede the onset of COVID-19 symptoms. Freeman and colleagues described retiform purpura as often occurring after COVID-19 symptoms (91%). In contrast, Galvan-Casas et al., which was published early in the pandemic in April 2020, showed that livedo (type not specified) and necrosis paralleled the onset of COVID-19 symptoms (86%). Given that the constellation of COVID-19 symptoms was not well-characterized early during the pandemic, this discrepancy may reflect differences in perception of symptom onset by clinicians and patients. Livedoid eruptions occur more often on the acral areas and last approximately 10 days, whereas retiform purpura has been described on the extremities and the buttocks. Although a pressure component may contribute to the development of retiform purpura, these lesions were also present in patients who were intermittently proned.[26,27] Many patients were started on therapeutic anticoagulation during their hospital course due to increasing d-dimer and suspected or confirmed thrombotic events.[20,28] Although anticoagulation in severe cases of COVID-19 has been shown to reduce mortality, both the exact dosing and the timing of anticoagulation initiation in these patients remain to be determined.[29,30] It is critical to consider the overall clinical picture and the patient's comorbidities, particularly bleeding risk, when determining the best course of treatment.

The pathophysiology of this coagulopathy is an area of active research. Complement-mediated microvascular injury appears to play an essential role in some cases. Exaggerated complement

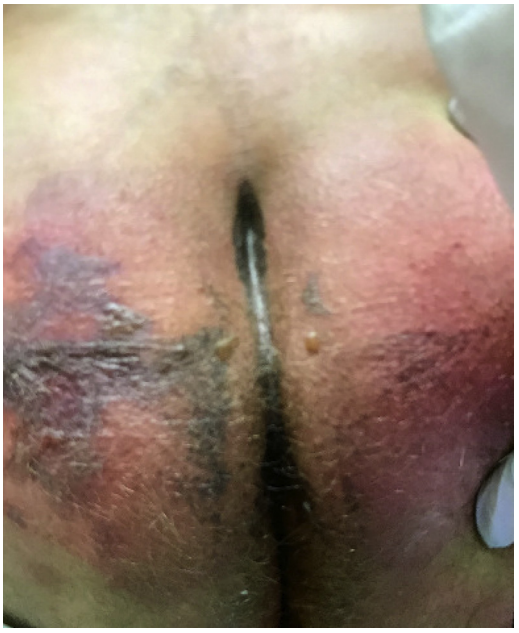

Fig. 3. Inflammatory retiform purpura in a COVID-19 patient complicated by ARDS. Biopsy revealed thrombotic. From Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. Transl Res. 2020;220:1-13.

activation has been implicated in severe COVID-19.[9,10] As the complement system links innate immunity to coagulation,[31] its overactivation could promote a thrombotic state in patients with severe COVID-19. Skin biopsies from patients with livedo racemosa and retiform purpura showed a pauci-inflammatory thrombogenic vasculopathy affecting capillaries, venules, and arteries with microvascular deposition of C3d, C4d, C5b-9, and MASP-2.[12,13,20] Excessive inflammation caused by a cytokine storm and the subsequent recruitment of immune cells has also been proposed as a potential cause of thrombophilic states in these patients.[32]

Pressure-Associated Ulceration and Necrosis

Critically ill hospitalized patients, including patients with COVID-19, are at an increased risk for sacral/buttock ulcerations caused by hospital-acquired pressure injuries (see **Table 1**). Ulcers described were often covered with black eschar with surrounding erythema and violaceous discoloration.[33] Livedoid plaques and retiform purpura, with biopsy showing thrombotic vasculopathy and evidence of pressure necrosis, were noted in some patients (**Fig. 3**).[12,33] Notably, patients with COVID-19 were found to develop these lesions earlier than other patient populations.

In addition, acrofacial purpura and necrosis associated with minor pressure injuries due to direct contact with medical devices, such as nasal cannulas, endotracheal tubes, or pulse oximeters, have been reported in patients with COVID-19.[26,27] Importantly, given that many patients with COVID-19 are placed in a prone position to improve oxygenation status, pressure-associated ulceration and necrosis can occur in a unique distribution such as the bilateral cheeks compared to the usual locations such as the sacrum and heels. As ulcerations can serve as portals of entry for microbes leading to infection, it is critical to monitor patients closely to prevent additional morbidity and mortality.

VIRAL EXANTHEM/INFLAMMATORY ERUPTIONS

Multisystem Inflammatory Syndrome in Children

In the early months of the pandemic, a novel pediatric illness characterized by a hyperinflammatory syndrome and hemodynamic shock was reported in children with SARS-CoV-2 infection.[34] This illness, now termed Multisystem Inflammatory Syndrome in Children (MIS-C), is characterized by fever, multiorgan dysfunction, and known or suspected exposure to SARS-CoV-2.[35] Many symptoms of MIS-C, including fever, mucocutaneous findings, and cardiovascular involvement, are similar to Kawasaki Disease (KD), a medium-vessel vasculitis presenting in children typically younger than 5 years.[32–34] However, unlike KD, MIS-C predominantly affects older children, with a median age of 10 years.[36] Furthermore, MIS-C has been associated with gastrointestinal symptoms, such as nausea and diarrhea—symptoms uncommon in KD.[37] Cardiovascular involvement in MIS-C manifests as left ventricular dysfunction, often necessitating pressure support and even extracorporeal membrane oxygenation in some cases. Coronary artery dilations, which are the cardiac hallmark of KD, are less common in MIS-C.[37,38]

Mucocutaneous findings are seen in most patients with MIS-C. Skin lesions include morbilliform, scarlatiniform, urticarial, and reticulated morphologies; patients with localized, acrofacial lesions and more widespread eruptions have been reported. Patients may also present with conjunctival injection, palmoplantar erythema, periorbital erythema and edema, and strawberry tongue, which is notably similar to the mucocutaneous examination in patients with KD,

necessitating a high index of suspicion for COVID-19–induced MIS-C in these patients.

Although COVID-19 infection in children is generally associated with a mild course with minimal or no symptoms, up to 68% of children with MIS-C required admission to a critical care unit, and 15% required ventilation[39] (see **Table 1**). In a prospective study of pediatric patients hospitalized with acute SARS-CoV-2 and MIS-C, lower absolute lymphocyte count and higher C-reactive protein were predictive of more severe MIS-C.[40] Although race/ethnicity was not predictive of disease severity, more than 75% of the cases reported to the Centers for Disease Control and Prevention have occurred in Hispanic/Latino or Black children.[40]

Treatment primarily consists of supportive care and intravenous immunoglobulin (IVIG) (2 gm/kg, based on ideal body weight), with low-moderate dose glucocorticoids (1–2 mg/kg/d) added for patients who have not developed shock or severe end-organ involvement.[41] Both interventions have been associated with shorter intensive care stays and hospitalizations.[42] Some guidelines have also recommended the use of immunosuppressive drugs like anakinra and tocilizumab.[43]

Morbilliform Eruptions

Morbilliform eruptions are characterized by pink to erythematous, blanching macules and papules caused by viral infections or drug hypersensitivity reactions. Morbilliform eruptions represent 21% to 23% of skin manifestations associated with COVID-19, making them among the most common rashes seen in patients with COVID-19[3,6,7,44] (see **Table 1**). Hospitalization rates for patients with morbilliform eruptions ranged from 45% to 80%, higher than the 30% to 38% seen in COVID-19 patients with nonmorbilliform cutaneous manifestations.[6,7] Morbilliform eruptions were shown to occur in 4 of 35 hospitalized COVID-19 patients (11.4%) who developed dermatologic findings.[5]

In both hospitalized and nonhospitalized patients, eruptions can occur concurrently or after other COVID-19 symptoms and last for an average of 1 week.[6,44,45] Truncal regions were the most commonly affected areas, followed by extremities. The most commonly reported symptom was pruritis. Patients who developed morbilliform eruptions were often in their fifties and sixties.[6,44,45] The overall rate for thrombotic events was 8% and for ARDS was 11%; 35% required ventilator support. The overall mortality of COVID-19 patients who developed morbilliform eruptions ranged from 2.6% to 3.7%.[6,44] Topical corticosteroids and antihistamines may be helpful in controlling morbilliform eruptions and associated pruritus in patients with COVID-19.[46,47] Systemic corticosteroids may also be considered in certain cases.[46,47]

Morbilliform eruptions are likely secondary to the immune response to viral infection. Skin biopsies show spongiosis, basal cell vacuolation, and perivascular lymphocytic infiltrate,[6,48] which are typically seen in other viral-induced skin lesions. However, a biopsy showing fibrin microthrombi within the small vessels has also been reported, suggesting a more complex pathophysiology may be operational in some cases.[49]

Drug hypersensitivity reactions are another cause of morbilliform eruptions and are likely implicated in some cases of morbilliform eruptions reported in patients with COVID-19. Indeed, 81.3% of patients with morbilliform eruptions were shown to have concomitant drug intake.[44] The most common culprit medications were chloroquine/hydroxychloroquine, lopinavir/ritonavir, and azithromycin. Similarly, patients who developed pruritic papular exanthems on receiving new medications for COVID-19 have been reported. In these cases, skin biopsies were compatible with drug reactions, and all cases improved with discontinuation of medication and use of systemic or topical corticosteroids.[50,51] Therefore, a strong suspicion of drug hypersensitivity should be considered in the evaluation of COVID-19–associated morbilliform eruptions.

Urticarial Eruptions

Urticarial eruptions are transient erythematous and edematous plaques of varying sizes mediated by mast cell histamine release in the superficial dermis.[52] Urticarial eruptions account for 13.5% to 26% of cases of COVID-19 cutaneous manifestations[1,3,4,6,7] (see **Table 1**). Hospitalization rates were 33% to 44%, similar to COVID-19 patients with non-urticarial cutaneous manifestations (34%–48%).[6,7] Most of the hospitalized patients needed only supplemental oxygen and did not develop ARDS or thrombotic events; only one fatality was recorded in the total 27 urticarial cases reported in this series.[6]

Urticarial eruptions most commonly occurred in adults in their forties. Urticarial eruptions often occurred on the trunk and extremities, with pruritis being the most common symptom and duration averaging 1 week.[6,7] Urticarial eruptions were rare before the onset of COVID-19 symptoms but have been observed concurrently (22%–61%) and after (35%–67%) the onset of symptoms. Of note, urticaria with or without angioedema has also been reported as the presenting feature or

as the only symptom of COVID-19, highlighting the importance of early recognition of urticarial rash in the diagnosis of COVID-19 as a means for limiting disease spread.[53–57] Some urticarial eruptions resolved without specific treatment, whereas others required antihistamine and/or low-dose systemic corticosteroids.[56,57]

Biopsy of a case of an urticarial plaque associated with COVID-19 revealed lymphocytic infiltrate with edema, spongiosis, lichenoid, and vacuolar interface dermatitis, consistent with viral exanthem.[58] Like morbilliform eruptions, the causes of urticarial eruptions in patients with COVID-19 must be interpreted with caution as some may represent reactions to medications. Viral infection can elicit a robust immune response and elevated proinflammatory cytokines. IL-6 level is notably elevated in patients with COVID-19.[59] As IL-6 can directly stimulate mast cell degranulation, elevated levels of proinflammatory cytokine could contribute to the development of urticaria in these patients. Also, as colocalization of SARS-CoV-2 glycoprotein with complement components has been demonstrated, it has been hypothesized that deposition of antigen-antibody complexes leading to complement activation and mast cell degradation could also cause urticaria in patients with COVID-19.[60,61]

Vesicular Eruptions

In a large cohort study, 7.2% of patients presenting with COVID-19–associated cutaneous manifestations were reported to have a vesicular eruption[5] (see **Table 1**). Two vesicular forms have been documented: a localized, monomorphic form found on the trunk and limbs and a diffuse, polymorphic form.[7,62] Most patients report minimal itching, which may help distinguish this eruption from the often very pruritic eruption of varicella.[63,64] Vesicular lesions associated with COVID-19 are most commonly seen in middle-aged men, with an average age of 45.6 $\pm$ 20 years.[6] The eruption is believed to be associated with early infection. The average latency time from onset of symptoms to rash is only 3 days (range -2 to 12 days); 15% of patients present with the lesions before any other COVID-19 symptoms.[6,45] In a cohort of Spanish patients, 32% with vesicular eruptions were admitted to a hospital, although only 6% required intensive care.[6] In a study comparing 24 COVID-19 patients with vesicular eruptions, of 6 patients with the localized pattern, 83.3% had concomitant COVID-19 pneumonia, compared to only 27.8% of those with the 18 patients who presented with the diffuse pattern; however, this was not statistically significant, likely due to small sample size.[62] Further research is required to fully elucidate the differences in the vesicular eruptions of those with severe COVID-19 requiring hospitalization compared with those with milder or asymptomatic disease. Lesions resolved in an average of 8 to 10 days without scarring.[62,64]

It has been proposed that the direct pathogenic effect of the SARS-CoV-2 virus on basal layer keratinocytes may lead to acantholysis and dyskeratosis.[63] To date, there has not been a report of the SARS-CoV-2 virus inside vesicles, identified by PCR assay or other methods, indicating that the infective potential via vesicles is likely minimal.

Erythema Multiforme-Like Eruptions

In April, a new pattern of erythema multiforme (EM)-like lesions in four adults hospitalized with COVID-19 was first described; since then, there have been numerous reports of EM-like lesions in children and young adults associated with SARS-CoV-2 infection[65] (see **Table 1**). Lesions appear as erythematous macules, papules, and plaques with crusted centers consisting of two (atypical targets) or three (typical targets) rings often observed on the extremities.[65–67] Lesions may be pruritic or painful.[51] Some patients present with oral mucosal involvement, including palatal macules and petechiae, and erosive cheilitis.[68,69] The mean age of patients with EM-like eruptions is 12.2 years with a male predominance (59.5%).[45] Latency of EM-life eruptions has been reported to range from only a few days to 3 weeks after the onset of initial COVID-19 symptoms.[44,65,66,68] A review of the literature found that EM-like eruptions have been described in up to 3.7% of patients hospitalized with COVID-19.[45] Of note, the incidence of EM-like eruptions may be under-reported as some studies group unspecific rashes of annular appearance into an "other rash" category.[70] Many patients were treated with systemic corticosteroids with the resolution of lesions.[71]

The pathogenesis of EM-like eruptions is not fully understood. Still, it is likely viral in etiology, although exposure to certain medications received in the treatment of other COVID-19 symptoms may play a role.

MISCELLANEOUS CUTANEOUS MANIFESTATIONS OF COVID-19 IN HOSPITALIZED PATIENTS

Sweet's Syndrome

Sweet's syndrome, also known as acute febrile neutrophilic dermatosis, is a nonvasculitic sterile neutrophilic dermatosis syndrome often

presenting with fever, arthralgias, and neutrophilia. Sweet's syndrome may be idiopathic, malignancy-associated, or drug-induced, and cases associated with viral infections have been reported.[72] There exists at least one case of a patient hospitalized with COVID-19 who developed Sweet's syndrome[73] (see **Table 1**). The patient developed numerous erythematous painful nodules on the scalp, extremities, trunk, and oral ulcers and fever; the lesions regressed without specific treatment as the patient recovered from COVID-19. Skin biopsy showed diffuse neutrophilic infiltration in the upper dermis with vascular proliferation. The elevated neutrophil count is a consistent finding in patients with COVID-19,[74] and this exaggerated neutrophilic response may have contributed to the development of Sweet's syndrome in this case.[73]

Petechiae and Purpuric Eruptions

Petechiae are nonblanching, nonpalpable pinpoint macules resulting from red blood cell extravasation; multiple petechiae coalesce to become purpura. Cases of petechiae and purpuric eruptions associated with thrombocytopenia have been reported in patients with COVID-19[75–79] (see **Table 1**). These eruptions often occurred after noncutaneous symptoms in hospitalized patients who were older and had had moderate to severe COVID-19. No deaths have been reported. IVIG, corticosteroids, thrombopoietin receptor agonists, and platelet transfusions have been used to manage these patients.[75–79] Although cases of thrombocytopenia secondary to DIC have been reported in COVID-19,[21] reported patients who developed petechiae and purpuric eruptions did not have DIC. Several mechanisms of thrombocytopenia have been proposed, including reduced platelet production due to cytokine storm, increased platelet destruction secondary to increased antibodies and immune complexes, and platelet aggregation resulting in microthrombi and platelet consumption.[80,81]

Perniosis ("COVID Toe")

Many cases of pernio or pernio-like lesions (red-purple tender papules typically affecting toes and fingers) have been reported typically as a late manifestation of confirmed or suspected COVID-19 infection. Although "COVID toe" is typically noted in young, healthy patients with mild or even asymptomatic COVID-19 infections, 16% of patients with "COVID toe" in one large international registry were hospitalized.[5] It should be noted, however, that misclassification of acral livedo or retiform purpura as "COVID toe" could occur given similar presenting locations and some overlap clinically (both present with purpura), especially if being evaluated and classified by nondermatologists. In one author's experience (J.H.), no cases of "COVID toe" or perniosis have been diagnosed in the inpatient setting of a large, academic hospital setting in New York City throughout the pandemic.

SUMMARY

Adults and children hospitalized with COVID-19 display a range of mucocutaneous eruptions, the diversity of which is likely due to the varying immune response generated in response to SARS-CoV-2 infection. In the hospitalized patient, livedo racemosa and retiform purpura were associated with more severe disease course, poorer prognosis, prolonged hospitalization, and higher mortality. In contrast, most viral exanthem and inflammatory lesions, such as urticarial and vesicular eruptions, were associated with a less severe COVID-19 disease course, although were nevertheless reported more frequently in the inpatient setting. One exception, however, is the presence of an inflammatory rash associated with MIS-C in the inpatient pediatric population, which has been associated with more severe COVID-19 disease and disease sequelae. Prompt recognition of the mucocutaneous manifestations presented in this article is paramount to facilitate timely diagnosis, proper treatment, and accurate prognostication of clinical course.

CLINICS CARE POINTS

- The two main categories of skin findings in patients with COVID-19 in the inpatient setting include vasculopathy -related (acral livedoid eruptions and retiform purpura) and inflammatory (vesicular, urticarial, erythema multiforme-like).
- Acral livedoid eruptions and retiform purpura in severe COVID-19 infections are often cutaneous manifestations of a systemic hypercoaguable state; and thus differ pathophysiologically and histopathologically from "COVID toe."
- Multisystem Inflammatory Syndrome in Children can prevent with a variety of mucocutaneous manifestations including variable rashes, conjunctival injection, palmoplantar erythema, and strawberry tongue.

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