

COVID-19 AND DERMATOLOGY (PART I): SKIN MANIFESTATIONS IN ADULTS AND CHILDREN WITH COVID-19 INFECTION

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ABSTRACT

Background/Aim: Since the announcement of SARS-CoV-2 virus infection (COVID-19) as a global pandemic at the beginning of March 2020 by the World Health Organization, dermatological manifestations of the infection have been encountered and publications on this topic have expanded. As an ongoing global pandemic, accumulation of new data has accelerated, and it has become a growing necessity to keep informed on current knowledge. The aim of these review series is to update published data on cutaneous manifestations of COVID-19 infection in adults and children (Part I) and adverse mucocutaneous reactions induced by medications and vaccines used for COVID-19 infection (Part II).

Materials and methods: Literature search was performed in the databases PubMed, Scopus, and Web of Science for the relevant studies, starting from the beginning of COVID-19 pandemic until October 2021. Research on animals, studies utilizing in vitro techniques and publications irrelevant to the study's framework were excluded.

Results: The skin manifestations of COVID-19 are frequent, polymorphic, and versatile. Herein, cutaneous findings liable to COVID-19 disease have been detailed as urticarial, maculopapular, vesicular, and vascular lesions and latest data on skin manifestations has been presented. Recently reported skin manifestations in children with SARS-CoV-2 infection, namely multisystem inflammatory syndrome, has also been covered as a topic.

Conclusion: There is a great amount of accumulated data regarding the cutaneous manifestations before, during and after COVID-19 infections. In the pandemic era, it is a major goal to elucidate pathognomonic, specific, or SARS-CoV-2 virus-related cutaneous signs and distinguish them from eruptions caused by medications, vaccines, and emotional stress. Owing to improvement and increased accessibility to diagnostic testing for COVID-19 infection and accelerated histopathological, immunological, and clinical investigations, the future holds promise for optimism in achieving that goal. Currently, it is known that cutaneous manifestations like vesicular and urticarial eruptions may also be present in asymptomatic individuals or develop before the onset of other symptoms of COVID-19 infection. In addition, some cutaneous manifestations may provide clues for prognosis. Furthermore, skin manifestations could be the sole clues in pediatric COVID-19 infections. Therefore, it is essential for physicians to update their knowledge regularly on skin manifestations of COVID-19 infection and mucocutaneous side effects of COVID-19 therapeutics and vaccines.

Keywords: Skin findings, COVID-19, adult, children.

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Introduction

Following the declaration of pandemic by the World Health Organization (WHO), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection-associated skin manifestations, mucocutaneous side effects of therapeutic agents and vaccines used for coronavirus disease 2019

(COVID-19) infection, or dermatoses related to personal protective equipment, masks, and hygiene-related dermatitis have been reported worldwide, especially in adults⁽¹⁻⁴⁾. Within the last year, dermatological findings in SARS-CoV-2 infected pediatric patients were also analyzed and published⁽⁵⁻⁸⁾. This manuscript presents a review of the literature on cutaneous manifestations of

COVID-19 infection in adults and children (Part I) and adverse mucocutaneous reactions induced by medications and vaccines used for COVID-19 infection (Part II).

Historical and epidemiological background

At the end of 2019, an RNA virus so-called SARS-CoV-2, a subgenus of beta-coronavirus, was identified as the offender of pneumonia cases in Wuhan, Hubei Province of Republic of China⁽⁹⁾. After an epidemic throughout China, the WHO declared COVID-19 as a pandemic on March 11, 2020. In the last month of 2020, new variants of SARS-CoV-2 were announced. Clinically confirmed cases of SARS-CoV-2 infection usually present with flu-like symptoms, gastrointestinal symptoms, and loss of smell and taste senses; however, approximately 20% of patients develop severe symptoms of lower respiratory system⁽¹⁰⁾. Symptoms due to involvement of other organ systems (nervous, endocrine, circulatory, immune, and even reproductive systems) have been documented⁽¹⁰⁾. Cutaneous involvement by SARS-CoV-2 infection was initially reported in Italy⁽¹¹⁾. Thereafter, the data on cutaneous manifestations of COVID-19 infection has rapidly accumulated with an accelerated publication rate and several hypotheses have been proposed on the pathogenetic mechanisms of these manifestations⁽¹²⁻¹³⁾. At the beginning of COVID-19 pandemic, the prevalence of skin manifestations has been reported as 0,2%⁽¹⁰⁾. However, a recent evidence-based review implied that the actual rate may be as high as 20,4%⁽²⁾. At the beginning of the pandemic, pediatric cases of COVID-19 infection were rare, and the infection was assumed to have a minor impact in this age group. However, as of today, pediatric cases account for %1-8 of all COVID-19 infections⁽⁵⁻⁸⁾.

Pathophysiology of skin manifestations

SARS-CoV-2 is an RNA virus; its genome encodes 16 non-structural proteins, all of which play specific roles in viral replication. Transmission is generally via respiratory droplets, but there is a latest testimony of fecal-oral transmission⁽¹⁴⁾. There is no proof of transmission through breast-feeding⁽¹⁴⁾. The virus binds to angiotensin-converting enzyme 2 (ACE2) receptors and the transmembrane serine protease 2 (TMPRSS2) in local cells⁽¹⁵⁾. The severity risk of COVID-19 infection is increased in the male gender, which may be attributed to upregulation of TMPRSS2 expression by androgens⁽¹⁶⁾.

SARS-CoV-2 virus exerts its negative effects on several organ systems through ACE2 receptors, found on numerous cells within the lungs, skin, cardiovascular, gastrointestinal, and renal systems⁽¹⁶⁾. In the skin, ACE2 receptors are highly expressed by the keratinocyte membranes at the basal layer of the epidermis, followed by eccrine sweat glands in the dermis^(17,18). The natural immune response to SARS-CoV-2 virus after exposure in a patient with non-severe disease involves immediate innate immune system activation, followed by activation of adaptive immunity within several days and acquisition of immunologic memory within several weeks. In contrast to other viral infections, IgM against COVID-19 does not appear earlier than IgA and IgG. A dysregulated immune response is the hallmark of severe SARS-CoV-2 infection, i.e., instead of targeting foreign pathogen-derived antigens, the immune system attacks host-derived self-antigens (autoreactivity)⁽¹⁶⁾. Recently published data suggests that cutaneous manifestations of COVID-19 infection could be ascribed both to interaction of virus with skin through the ACE2 receptors and to dysregulated, hyperactive immune response with complement activation or vascular injuries⁽¹⁶⁾.

COVID-19 skin manifestations in adults

The skin manifestations of COVID-19 are frequent, polymorphic, and versatile⁽²⁻⁴⁾. The potpourri of cutaneous clinical manifestations comprise maculopapular, morbilliform, purpuric, vesicular, digitate papulosquamous, erythematous, urticarial, acral lesions, chilblains, erythema multiforme, periorbital erythema, alopecia, erythronychia etc⁽¹⁻⁴⁾. Some studies classified skin manifestations of COVID-19 infection according to morphology and histopathology^(3,10,11,19-21). The following published studies were based on these classifications and assessed the direct and indirect impact of virus on cutaneous manifestations, the influence of comorbidities on skin findings, and correlation between disease severity and skin involvement^(1,13,22,23).

The data on cutaneous manifestations of new SARS-CoV-2 variants is scarce (24,25). In a cross-sectional study involving 144 hospitalized patients infected with new SARS-CoV-2 variants, skin manifestations were less frequent. This dilemma has been explained by variations in SARS-CoV-2 antigenicity altering the immunological response or reducing its cutaneous tropism⁽²⁴⁾.

Corroborating this hypothesis, the delta variant of SARS-CoV-2 displays vascular cutaneous lesions, implying a tropism for vascular system⁽²⁵⁾.

Urticarial rash

Urticaria and angioedema can be triggered by infections, especially with viruses such as cytomegalovirus, herpesvirus, and Epstein-Barr virus. However, establishing a definitive association and proving the pathophysiological interaction is difficult in clinical practice⁽²⁶⁾. Urticaria is one of the most frequently reported skin findings in patients with COVID-19 infection and poses as a pruritic eruption distributed over the trunk, thighs, and sometimes facial and acral regions. The prevalence of urticaria in COVID-19 infection varies from 7 to 40% in different publications^(21,27,28). Urticarial eruption has a predilection for the female gender and tends to affect patients between 45 to 65 years of age^(27,29). Urticaria risk is higher before the onset and during the time of COVID-19 diagnosis^(27,29). In one study, urticarial rash was accompanied by symptoms such as cough, dyspnea and fever, in decreasing order of frequency. Anosmia, ageusia, chills, and dizziness were other concomitant symptoms^(3,4). COVID-19-associated urticaria was reported to persist for a median of 4 days⁽³⁰⁾. Histopathological examinations expose a portrait similar to idiopathic urticaria, i.e., a perivascular lymphocytic infiltrate, various eosinophils, and upper dermal edema, without virus-induced cytopathic alterations^(13,31). Treatment of urticaria in patients with COVID-19 consists of low-dose systemic corticosteroids, combined with antihistamines. The duration of corticosteroid treatment should be confined to the period elapsed until the suppression of symptoms⁽³²⁾. Urticaria associated with COVID-19 infection might stem either from viral IgM/IgG cross-reacting with IgE on mast cell surface causing mast cell degranulation, or from medications used for COVID-19 treatment⁽³³⁾. Regardless of the cause, COVID-19 infection should be kept in mind in any patient presenting with an urticarial eruption in the pandemic era.

Maculopapular erythematous rash

Maculopapular (morbilliform) rashes are characterized by erythematous skin eruptions composed of flat macular and raised papular lesions. In the dermatology arena, maculopapular rashes usually denote an underlying viral infection or a drug eruption. In COVID-19-infected patients, maculopapular rash has the highest prevalence

among the list of cutaneous manifestations (40-70% of cases), although it has unfortunately been reported with inconsistent terminology (erythematous eruptions, maculopapular eruptions, macular erythema, papulosquamous eruption^(4,28,34). COVID-19-associated maculopapular rashes have been described especially in elderly patients, with no gender predilection. The lesions are concentrated on the trunk and may be accompanied by pruritus and pain⁽³⁴⁾. The maculopapular rash has its onset usually after COVID-19-related symptoms and often appears in patients with intermediate severity of the disease^(4,35). In contrast to urticarial eruptions, half of patients with maculopapular eruptions require hospital admissions and 2.8% of them eventually entail care in intensive care units because of severe COVID-19 pneumonia⁽¹⁹⁾.

According to Catala et al., the most frequent symptom accompanying maculopapular rashes was fever, followed by cough, dyspnea, asthenia and others⁽³⁶⁾. The median duration of maculopapular rash has been recorded as 7 days (35). Histopathological examination displays a superficial perivascular dermatitis with mild spongiosis, lymphocytic vasculitis with rare microthrombi, dyskeratotic necrotic keratinocytes (Grover-like features^(37,38). Treatment is wavered according to severity of the rash. Topical and systemic corticosteroids, antihistamines and vitamin C have been recommended⁽³²⁾. The main differential diagnostic considerations encompass cutaneous drug reactions and skin eruptions caused by other viruses. In the pandemic era, COVID-19 infection should be born in mind in any patient presenting with a maculopapular eruption.

Vesicular eruption

Vesicular eruptions are characterized by collections of transparent fluid-filled epidermal blisters, each having a diameter of < 0.5 cm. They are usually encountered during viral infections, such as herpes, varicella, echovirus, coxsackievirus etc.⁽³⁹⁾. Vesicular eruptions caused by COVID-19 infection could be categorized into diffuse polymorphic and localized monomorphic patterns, according to morphology⁽⁴⁰⁾. The diffuse polymorphic pattern (papules, vesicles, and pustules) simulates “varicella”, and hence it has been termed as ‘varicella-like eruption’. Polymorphic vesicular eruption of COVID-19 infection can be distinguished from true varicella by predominantly truncal involvement, scattered distribution, and mild/absent pruritus in the former⁽⁴¹⁾.

On the other hand, the localized monomorphic pattern typically involves the trunk and back and mimics Grover Disease (transient acantholytic dermatosis), a benign skin condition with crusted papulovesicles^(40,42-44). The prevalence of vesicular eruptions in COVID-19 infection ranges from 9 to 15% in different studies^(21,45,46). They are usually encountered in male patients at their 5th to 7th decades of life; however, vesicular eruptions have also been observed in children^(3,34,45). The data on onset and duration of vesicular eruptions is inconsistent across different studies. Vesicular eruptions in COVID-19 infected patients are frequently confronted during early-stage infection, but they may also develop before the onset of SARS-CoV-2 infection symptoms. They generally last about 10 days^(21,34,45,46). Some reports have mentioned about vesicular rash accompanying mild and moderate symptoms of COVID-19 infection (most commonly fever, cough, headache, weakness and coryza)^(41,46). Histopathological examination discloses acantholysis and dyskeratosis associated with the presence of a unilocular intraepidermal vesicle in a suprabasal location. Mahe et al. detest the term “varicella-like rash” for vesicular eruptions of COVID-19 infection and propose “COVID-19 associated acantholytic rash” as a more appropriate term. On the other hand, other reports proclaimed the presence of acantholysis and ballooning degeneration of keratinocytes^(40,47). There is no standardized treatment for vesicular eruptions of COVID-19 infection. Because of short healing interval and mild pruritus, “wait-and-see” strategy might be judicious^(3,32). In the pandemic era, vesicular rashes might be indicative of COVID-19 infection. Nevertheless, Tzanck smear, viral culture, PCR of vesicle fluid, serologic tests and skin biopsy might be required to exclude other viral infections⁽⁴³⁾.

Vascular lesions

Vascular injury and coagulation tendency frequently convoy COVID-19 infections⁽²⁸⁾. Cutaneous findings linked to vascular involvement comprise petechia, purpura, livedoid and pernio-like lesions. Unfortunately, in the relevant literature, acro-ischemic lesions and pernio were used synonymously and collectively referred to as “COVID fingers”, but these two terms are far from being identical^(40,48). The acro-ischemic lesions can be classified within the spectrum of vaso-occlusive lesions, like livedo racemosa (secondary livedo reticularis) and thrombotic retiform purpura. The

vaso-occlusive lesions of COVID-19 infection have a very low prevalence among the list of cutaneous manifestations and primarily seen in critically ill elderly patients with disseminated intravascular coagulation (DIC) or elevated D-dimer levels^(19,48,49). Apart from vaso-occlusive lesions, vascular skin manifestations of COVID-19 infection rank the second most frequent cutaneous findings after maculopapular eruptions and has been discussed in separate below.

Petechiae and purpura

Petechia (a pinpoint round macule less than 4 mm in diameter) and purpura (around macule 4 to 10 mm in diameter) result from visible intracutaneous hemorrhage. They can arise because of hematological disorders, or problems related to vascular wall integrity or blood flow. They can be observed in some viral infections (enterovirus, parvovirus B19) as well. The prevalence of petechiae and purpura in COVID-19 infection has been reported as 3-4%^(50,51). The predominant sites of distribution are diffuse involvement or solely extremities for petechial lesions, and lower extremities and buttocks for purpuric lesions⁽⁵¹⁾. COVID-19-infected patients with petechiae and purpura are largely above the middle age with no gender predilection⁽⁵²⁾. Generalized petechiae and purpura are observed in the most severe forms of COVID-19 infection^(4,52). The mortality rate is high in COVID-19 patients presenting with petechiae and purpura, and there is no specific treatment^(4,33). Although petechial and purpuric lesions can be observed at any time throughout the course of SARS-CoV-2 infection, they might signal early infection^(51,53,54). In the pandemic era, any patient presenting with petechiae, purpura and fever should be tested in order to rule out SARS-CoV-2 infection^(51,53,54).

Livedo reticularis-like lesions

Livedo reticularis is usually a benign net-like, red-blue reticulated discoloration of the skin. Underlying factors are generally rheumatological diseases, drugs, and infections⁽⁵⁵⁾. Livedo reticularis-like lesions, located especially on dorsal hands and feet, forearms, chest, and legs, are encountered with a prevalence of 3.5% in COVID-19 infections^(51,56). They can develop at any time during SARS-CoV-2 infection, but onset usually shows concordance with other systemic symptoms of COVID-19. The average duration of livedo reticularis-like lesions is 9 days; however, the course may be sustained

with progression to purpuric and papulonecrotic cutaneous vasculitis in 0.6% of cases, signifying a vaso-occlusive complication⁽⁵⁶⁾. Livedo reticularis-like lesions associated with hematuria portend a higher risk of renal damage, the major cause of mortality in afflicted patients^(12,51,56). Mild cases might be treated with systemic antibiotics and topical corticosteroids. Severe cases prompted by vaso-occlusion might benefit from COVID-19 standard care, including low-molecular-weight heparins and systemic corticosteroids⁽³²⁾.

Pernio (chillblain)-like acral lesions

Pernio is an idiopathic cold-induced inflammatory condition, usually secondary to underlying rheumatologic disorders, hematologic malignancies, genetic disorders, and viral infections, such as Epstein-Barr virus. Clinically it manifests as erythematous to violaceous macules, papules, and plaques with swelling, pruritus, pain, and burning sensation on cold-exposed acral regions like fingers and toes. Lesions may exhibit blistering or ulceration⁽⁵⁷⁾. Before COVID-19 pandemic, reports on pernio were scarce. The publications boosted along with the pandemic^(50,58). The prevalence of pernio-like lesions in COVID-19 infection has been reported as 14–72% in different studies^(49,59,60). Interestingly, pernio-like lesions in COVID-19 infection are not provoked by cold exposure and show a tendency for localization to fingers and toes^(4,61). Cappel et al. granted that clinical presentation is similar to ordinary chilblain in 63% of cases and that feet were involved in 94% of cases⁽⁶²⁾. Pernio-like lesions show no gender predilection and are usually confronted in young patients with mild COVID-19 infection. The duration of pernio-like lesions is prolonged; lesions persevere for approximately 2 to 8 weeks^(1,61). Persistent (longer than two months) and recurring variants in the absence of reinfection, have been reported^(1,61). Histopathology of pernio-like lesions is similar to idiopathic or systemic disease-related chilblains and encompasses perivascular lymphocytic infiltrate with perieccrine accentuation, dermal edema, and absence of overt epidermal necrosis, with exceptional presence of apoptotic keratinocytes^(60,63). Histopathological studies have clarified that in contrast to vaso-occlusive lesions, pernio-like lesions are primarily inflammatory, nonischemic and not reflective of systemic coagulopathy^(59,60,63). Yet, biopsy may rarely disclose microthrombi in bullous or necrotic clinical variants of pernio-like lesions⁽⁴⁹⁾.

Remarkably, some studies have demonstrated positive immunostaining for anti-SARS-CoV-2 and viral spike protein in skin biopsy specimens of pernio-like lesions⁽⁶⁴⁾. These findings suggest that SARS-CoV-2 might directly be incriminated in the occurrence of pernio-like lesions. Although such lesions tend to resolve spontaneously, topical steroids and antibiotics might be utilized for treatment⁽³²⁾.

Other skin lesions

Other skin manifestations reported in patients with COVID-19 infection include vasculitis, periorbital erythema, pityriasis rosea-like lesions, Gianotti-Crosti-like rash, acute generalized exanthematous pustulosis-like rash, symmetrical drug-related intertriginous and flexural exanthema-like rash, erythema elevatum diutinum-like rash, aphthous lesions, ulcerated or pigmented mucosal lesions, zona zoster, alopecia, nail changes etc^(1-4,36,65,66). Compared to evidence-based skin manifestations of COVID-19 infections reviewed above, there is a serious lack of proof on direct association of these rare skin manifestations with SARS-CoV-2 infection, itself. Rather they might represent coincidental skin findings in COVID-19-infected patients or arise from immune alterations caused by COVID-19 infection or develop as adverse effects of medications used for treating COVID-19 infection. Furthermore, the role of emotional stress in the occurrence of skin lesions during the pandemic cannot be overlooked.

Skin manifestations of COVID-19 in pediatric patients

At the beginning of COVID-19 outbreak, reports on pediatric cases were scant and early reports alluded to a low prevalence of COVID-19 infection in children⁽⁶⁷⁾. Today, evidence-based reviews indicate that 1 to 5% of COVID-19-positive patients are children and that the clinical presentation, course, and outcome of the infection in children differ from those in adults^(68,69). Overall, pediatric patients have milder disease and scarcer deaths, as compared with adults⁽⁶⁹⁾. In children, dermatological manifestations may be the sole clues for COVID-19 infection. The prognosis in COVID-19-infected children with skin manifestations is better, as compared to those without skin manifestations⁽⁷⁰⁾. There are also some clinical and histopathological discrepancies between adults and children, in terms of skin manifestations of COVID-19 infection. Urticaria in children with COVID-19 infection is usually non-pruritic^(7,71).

Varicella-like papulovesicular rash in children with COVID-19 infection is typically monomorphic with frequent mild itching^(7,38,41,71). Pernio-like lesions are more common in adolescent patients with good health and rarely observed in children younger than 10 years of age^(6,72). The majority of children with pernio-like lesions are asymptomatic and do not experience COVID-19 symptoms^(6,72,73). Some cutaneous manifestations, such as erythema multiforme (EM), and Kawasaki disease-like inflammatory multisystemic syndrome, are more common in children.

Erythema multiforme

EM is a hypersensitivity reaction, that presents with pathognomonic symmetrical, targetoid erythematous lesions. The most common causes are infections, followed by drugs⁽⁷⁴⁾. EM-like eruptions have been reported both in adults and children with COVID-19 infection^(21,75). The predominant localization in COVID-19-related-EM are truncal and acral regions⁽⁷⁶⁾. In one report, a skin biopsy revealed positive immunostaining for SARS-CoV-2 spike protein in the endothelium⁽⁷⁷⁾. COVID-19-related-EM in children is frequently asymptomatic or exceptionally associated with mild pulmonary or gastrointestinal symptoms⁽⁷⁷⁾.

Kawasaki disease-like inflammatory syndrome (multisystem inflammatory syndrome in children) (MIS-C)

Kawasaki disease (KD), also known as ‘mucocutaneous lymph node syndrome, is an acute febrile disease with unknown etiology. Bacterial and viral infections (such as common seasonal coronavirus) have been suspected as triggering factors. It is one of the most common forms of vasculitis in children. Its diagnosis relies on clinical and laboratory criteria⁽⁷⁸⁾. Throughout the second half of the first pandemic wave, several reports have been published on a severe multisystemic condition imitating KD in children with COVID-19 infection. The US Centers for Disease Control and Prevention (CDC) issued a health advisory on May 14, 2020, that outlines the case definition of MIS-C⁽⁷⁹⁾. The case definition of MIS-C is shown in Table I. Even though MIS-C shares some clinical features with KD, only 50-52% of cases fulfill KD criteria^(80,81). Accumulated data show that children with MIS-C are older than children with KD. In contrast to KD, which is predominant in Asian children as a demographic feature, MIS-C has generally been

reported from African-American and Hispanic races 882,83). Clinically, gastrointestinal symptoms are more frequent in MIS-C; however, cutaneous manifestations are similar to KD (non-exudative conjunctivitis, polymorphic rash, perineal or face desquamation, erythema and induration of hand and feet)^(80,81,84). Inflammatory markers are elevated in almost all patients (CRP, ESR, neutrophil count and ferritin). More than %80 of children with MIS-C require hospitalization in intensive care units. Hopefully, recovery will be uneventful and the current mortality rate is 2% (84). MIS-C can be managed by using aspirin, intravenous immunoglobulin, systemic antibiotics, and corticosteroids^(80,84).

Patient <21 years of age	
-Fever	≥38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours
-Laboratory evidence of inflammation (Including, but not limited to, one or more)	Elevated. • C-reactive protein (CRP), • Erythrocyte sedimentation rate (ESR), • Fibrinogen, • Procalcitonin, • D-dimer, • Ferritin, • Lactic acid dehydrogenase (LDH), or Interleukin 6 (IL-6) • Neutrophils, Reduced. • Lymphocytes • Albumin
-Evidence of severe illness requiring hospitalization	☐ • Cardiac
-Multisystem (≥2) organ involvement	☐ • Renal
	☐ • Respiratory
	☐ • Hematologic
	☐ • Gastrointestinal
	☐ • Dermatological
	☐ • Neurological
-No alternative plausible diagnosis And	
-Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test or exposure to suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms	

Table 1: The case definition of MIS-C issued as a health advisory by CDC.

Conclusion

There is a great amount of accumulated data regarding the cutaneous manifestations before, during and after COVID-19 infections. In the pandemic era, it is a major goal to elucidate pathognomonic, specific, or SARS-CoV-2 virus-related cutaneous signs and distinguish them from eruptions caused by medications, vaccines, and emotional stress. Owing to improvement and increased accessibility to diagnostic testing for COVID-19 infection and accelerated histopathological, immunological, and clinical investigations, the future holds promise for optimism in achieving that goal. Currently, it is known that cutaneous manifestations like vesicular and urticarial eruptions may also be present in asymptomatic individuals or develop before the onset of other symptoms of COVID-19 infection.

In addition, some cutaneous manifestations may provide clues for prognosis. Furthermore, skin manifestations could be the sole clues in pediatric COVID-19 infections. Therefore, it is essential for physicians to update their knowledge regularly on skin manifestations of COVID-19 infection and mucocutaneous side effects of COVID-19 medications/ vaccines.

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