Skin manifestations in patients with coronavirus disease 2019

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Purpose of review
Coronavirus disease 2019 (COVID-19) is a well established respiratory tract illness. Recent studies in adults and children have shown an increasing number of patients reporting polymorphic cutaneous manifestations during COVID-19, including different types of rashes, from maculopapular, vascular, vesicular to atypical forms.

Recent findings
Although pathogenesis of skin manifestations is still not fully understood, it has been proposed that cutaneous involvement during COVID-19 may be the results of the activation of the immune response against SARS-CoV-2, the reactivation or co-infection of herpesviruses or drug hypersensitivity.

Summary
According to available literature, skin manifestations in patients with COVID-19 may be categorized on the basis of their clinical presentations as follows: erythematous rashes, lesions of vascular origin, vesicular rash, urticarial rash and acute generalized exanthematous pustulosis (AGEP), erythema multiforme and other polymorphic erythema/atypical reactions. Prompt recognition of these cutaneous manifestations represents a crucial point to facilitate diagnosis and management of COVID-19 patients.

Keywords
coronavirus disease 2019, cutaneous manifestations, erythematous rashes, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), vascular lesions, vesicular rashes

INTRODUCTION

Coronavirus disease 2019 (COVID-19) primarily manifests as a lung infection, with most symptomatic patients presenting with fever, cough and dyspnoea [1▪]. However, COVID-19 has also significant extrapulmonary complications affecting most organ system [2,3], such as the the central nervous system [4], gastrointestinal tract [5], the cardiovascular system [6] and the skin [7].

Regarding dermatological manifestations, recent findings suggest that the skin is involved in about 1–20% of the patients [8▪▪,9–11,12▪▪,13], with skin manifestations related to COVID-19 generally being wide ranging and heterogenous [3,8▪▪,11,12▪▪,13]. According to published literature [7,14▪▪], skin manifestations in patients with COVID-19 may be categorized on the basis of their clinical presentations as follows: erythematous rashes, lesions of vascular origin, vesicular rash, urticarial rash and acute generalized exanthematous pustulosis (AGEP), erythema multiforme and other polymorphic erythema/atypical reactions.

In this review, we summarize the current literature regarding skin involvement in COVID-19 patients. We will also discuss the current knowledge about potential pathogenetic mechanisms, prognostic aspects as well as macroscopic and

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KEY POINTS

- Skin manifestations have a significant prevalence in those with coronavirus disease 2019.
- The most common skin manifestations include erythematous rashes, lesions of vascular origin, vesicular rash and urticarial rash.
- Each skin manifestation has been associated with a different severity and clinical course of COVID-19.

microscopic features of cutaneous manifestations during COVID-19 disease.

GENERAL ASPECTS INVOLVED IN THE PATHOGENESIS OF CORONAVIRUS DISEASE 2019 SKIN MANIFESTATIONS

The pathogenesis of skin manifestations in patients with COVID-19 has not yet definitively understood. ACE-2 receptors, by which the virus gains entry, are located through the epithelium of different organs including the subcutaneous fat and the epithelial cells of the skin [15], where their density of expression plays a significant role for inflammatory response. Direct viral invasion to the epithelium [16,17] can result in a direct tissue injury with lymphocytic endotheliitis, necrosis and microvascular disfunction [18,19]. In addition, virus-induced cytopathy and the persistence of the virus in the skin of COVID-19 patients may also been associated with the development of skin manifestations, as suggested by recent studies reporting positive Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) real-time PCR (RT-PCR) in skin samples of COVID-19 patients with generalized macular eruption [20] or purpuric eruption [21]. The role of viral persistence has also been advocated in studies using immunohistochemistry technique showing the presence of viral inclusions and spike protein in endothelial and epithelial cells of a significant proportion of COVID-19 patients presenting chilblain like lesions [22,23]. The cytokine storm and complement activation have also been implicated in the pathogenesis of COVID-19 skin manifestations. Viral entry initiates a chemokine response, attracting T cells that mediate the initial inflammatory response. Increased levels of pro-inflammatory cytokines, such as interleukin (IL)-2, IL-7, IP10, TNF-α, IL-6 have been observed within the skin of COVID-19 patients and their levels have been associated with disease severity and immune response. Recent works have demonstrated that higher levels of IL-6 and granulocyte macrophage-stimulating factor (GM-CSF), further promote vascular damage [24–26].

Lastly, complement deposition (C5b-C9 and C4d) in dermal capillaries described in different COVID-19-related dermatological manifestations (e.g. retiform purpura) [27,28] seems to play a significant role in mediating tissue damage, coagulation cascade activation and microvascular injury.

SKIN MANIFESTATIONS IN PATIENTS WITH CORONAVIRUS DISEASE 2019

Although the timing of skin involvement in COVID-19 patients is difficult to ascertain [8▪▪,29,30], clinicians should be aware that almost 10% of the patients develop skin manifestations before the onset of respiratory illness, with cutaneous signs that can potentially appear from 3 days before to several days after the diagnosis of COVID-19 [12▪▪,31]. Moreover, not only severe COVID-19 patients may present skin manifestations, but also paucisymptomatic or asymptomatic patients may be involved, as suggested by a retrospective analysis on skin biopsies performed in Milan (Italy) before official COVID-19 outbreak, in which COVID-19 was found in almost asymptomatic patients[32▪▪,33,34].

In this section, we will briefly summarize the clinical manifestations as well as the etiopathogenetic and histological findings of COVID-19 skin involvement.

Erythematous rashes

Erythematous rashes are the most common cutaneous manifestations observed in patients with COVID-19 [12▪▪,35]. Several different patterns of rashes have been described in this group of COVID-19 skin manifestations, mainly including the maculopapular, the papular, or the papulosquamous one. Other less common subpatterns resembling pityriasis rosea, Grover disease and Symmetrical Drug-Related Intertriginous and Flexural Exanthema (SDRIFE) have also been reported in some case reports [36–38]. Although the frequency of the different patterns of exanthema varies among the published data, the maculopapular is the most common, being observed up to ∼70% of COVID-19 patients with erythematous rashes [39,40▪].

From a clinical point of view, these manifestations resemble those of conventional urticarial, common viral exanthema, erythema multiforme or drug-induced exanthema. They usually occur concurrently or after other clinical manifestations related to COVID-19 and generally last for an average of 8 days [12▪▪,35,41–43]. Positivity for COVID-19 and the prior medical history drive the diagnosis but a reactivation of previous HSV, VZV or HHV-6 has been also postulated [14▪▪,18,44]. However,

regarding the pathogenic mechanism of erythematous rashes, other several hypotheses have also been taken into account. In particular, some authors suggest that erythematous rashes are the result of an adverse reaction to drugs administered during the SARS-CoV-2 infection (e.g. hydroxicloroquine, lopinavir/ritonavir) [14▪▪], as is in the case of ampicillin rash during Epstein–Barr virus infection [45]. However, a drug reaction was not confirmed in other studies [46,47], in which morbilliform rash developed in COVID-19 patients without taking any medications [35]. As an alternative hypothesis, erythematous rashes can also represent the result of an immunological activation against the virus, having similar characteristics to those observed in other viral exanthems [43].

As for microscopic feature, skin biopsy performed on COVID-19 patients with maculopapular or erythema multiforme-like rash showed a diffuse interface dermatitis with necrotic keratinocytes and a dermal infiltrate particularly around the eccrine glands' ducts and acrosyringeal ducts (so called 'Erythema multiforme-like pattern'). Interestingly, nests of Langerhans cells in the epidermis and abnormally dilated capillaries engorged with red blood cells were constantly observed. COVID-19-associated papulovesicular rash showed prominent acantholysis and dyskeratosis associated with intraepidermal vesicles, and in some cases, ballooned keratinocytes. Many patients presenting erythematous-urticarial lesions show on histology dermal edema with highly dilated capillaries (in fully developed cases engorged with red blood cells), perivascular lymphocytes and interstitial infiltration of eosinophils together with a mild periglandular lymphoid infiltrate surrounding the dermal ducts and eccrine glands (so called 'Mini-chilblain-like pattern') [32▪▪,33,48].

Vascular lesions

Vascular lesions associated with COVID-19 are the second most common skin manifestations described in the medical literature [12▪▪,33,35,49]. There are different patterns belonging to this group: chilblain-like rashes (also known as pernio-like lesions or pseudo chilblain) and other skin findings underlying variable degree of ischemia, such as livedo racemosa, retiform purpura or acral ischemia. Chilblain-like lesions (rarely bullous) represent late manifestations of COVID-19 and, in contrast to other COVID-19-related skin manifestations, they are more often reported in children and young adults. These manifestations usually occur later in the course of COVID-19 and last longer (mean 12.7 days) than erythematous rashes [12▪▪]. As for clinical manifestations, pain or burning sensation as well as pruritus have been commonly recorded in patients with chilblain-like lesions. Regarding their pathogenesis, they usually appear in patients without systemic symptoms or with relatively mild COVID-19 disease. Accordingly, several authors suggest that these skin lesions may be a surrogate of a marker of a robust and effective host viral response, thus limiting SARS-CoV-2 replication [14▪▪,35]. In this sense, IFN-1, a potent cytokine-mediating inflammatory response in young patients, is considered to play a crucial role in producing chilblain-like lesions in COVID-19.

Histology shows a lymphocytic vasculopathy around medium-calibre and small-calibre vessels associated with microthrombi and with a dense peri-glandular lymphocytic infiltration and variable necrosis of the epidermis (so called 'Chilblain-like pattern') [32▪▪,48]. These findings, together with the fact that the lesions occur in climates without such cold temperature to justify their occurrence [12▪▪,35,50], further support the hypothesis that they are primarily chilblains related to a systemic illness, as the chilblain lupus erythematosus.

Livedo reticularis/racemosa-like pattern is rarely found in COVID-19 patients (from 0.6 to 3.5% of different series) but livedo racemosa-like lesions have been frequently reported in patients with severe coagulopathy [7,51]. Histology shows a pauci-inflammatory microthrombotic vasculopathy, similar to the 'Chilblain-like pattern' [32▪▪,48]. Other purpuric/vasculitic lesions include a broad spectrum from a petechial rash, purpura, palpable purpura, dengue-like eruption and even haemorrhagic blisters. Necrosis (and rarely also gangrene) has been reported in patients with severe coagulopathy. Purpuric/vasculitic lesions may be localized particularly on acral sites, or disseminated and are more frequent in elderly patients with severe COVID-19 disease and high risk of mortality. Histopathology reveals perivascular dermatitis, large nets of Langerhans cells, mast cell hyperplasia, lymphocyte infiltration around swollen blood vessels with all the features of a leukocytoclastic vasculitis, with variable degree of severity [14▪▪,18,44,51,52]. Erythrocyte extravasation and intravascular microthrombi are also present, with variable degree of severity. These features correlated with different degree of thrombosis [35,48,53,54]. These vascular manifestations are probably because of multiple cytokines releasing and coagulation disorder with microvascular injury and thrombosis [27,53].

Vesicular rash

Several authors reported vesicular rashes up to 10% of patients with COVID-19 skin manifestation, with itchy as major symptom. The median time from

COVID-19 symptoms to vesicle eruption was 14 days (range 4–30 days) [12▪▪,31] and, in most cases, the rashes were not considered as drug-related. [40▪]. Clinically, two different patterns of vesicular rashes have been described: a localized one (~25% of the cases) with monomorphic lesion and a diffuse one (~75% of cases), characterized by distinct primary skin lesions [7]. In the localized pattern, lesions were described as monomorphic and involved especially the trunk region. On the other hand, in the diffuse pattern, the lesions were polymorphic and included papules, pustules and vesicles localized at different body area [40▪]. The pathogenesis of vesicular rashes during COVID-19 has not been fully elucidated. A fascinating hypothesis suggest that infection with SARS-CoV-2 could create a susceptibility for latent herpes virus reactivation in skin area with a prior damage. In contrast, healed lesions because of another pathogen could contribute to the appearance of SARS-CoV-2-related vesicular manifestations. In other words, the affected area could represent a 'locus minoris resistentiae' in which the SARS-CoV-2 could facilitate the onset of pathologic lesions, in accordance with a mechanism previously known as 'Wolf isotopic response' and currently reproposed as a true variant of Koebner phenomenon [55–57]. As for histological findings, vesicular rashes showed prominent acantholysis and dyskeratosis associated with intraepidermal vesicles, and in some cases, ballooned keratinocytes. Lymphocytic perivascular infiltrate, vascular leak, dyskeratotic keratinocytes and edema with vacuolar interface dermatitis were also described [35,48,54].

Urticarial rash

Urticarial eruptions were also described, with a wide incidence rate, ranging between 10 and 20%, of the cases [8▪▪,12▪▪,31,35,48,54,58]. Several hypotheses exist to explain the pathogenic mechanisms of these manifestations. In some cases, skin biopsy was consistent with an adverse reaction to drug taken during the infection, whereas some other developed them without taking any medication. More recently, new data are emerging about the direct skin localization of the virus [59] also in cases of improvement without drug discontinuation [59–61].

Erythematous-urticarial lesions submitted to histopathological examination, showed the presence of dermal oedema together with highly dilated capillaries (in fully developed cases engorged with red blood cells), perivascular lymphocytes and interstitial infiltration of eosinophils. A mild peri-glandular lymphoid infiltrate surrounding the dermal ducts and eccrine glands (so called 'Mini-chilblain-like pattern') was also reported [32▪▪,33,48].

Acute generalized exanthematous pustulosis, erythema multiforme and other rare/atypical reactions

AGEP is characterized by a sudden onset of widespread nonfollicular sterile pustules arising within large areas of oedematous erythema. AGEP has been primarily described in patients treated with hydroxychloroquine [62,63] and it usually occurs after 48 h of ingestion, often with an acute onset of fever and leucocytosis. A variant of the AGEP named Generilized Pustular Figurate Exanthema (GPFE) has been also described in COVID-19 patients receiving hydroxychloroquine [64,65]. GPFE initially present as an urticaria with the following development of nonfollicular pustules and later characterized by targetoid and arcuate plaque [64,65].

Erythema multiforme pattern has also been described during the course of COVID-19. All patients developing erythema multiforme were hospitalized and received different drugs, including hydroxychloroquine, antibiotics and lopinavir/ritonavir. The full understanding of the pathogenesis of erythema multiforme remains unknown. A possible role of delayed immune response to the virus has been advocated [66].

Other rare/atypical skin manifestations

Other rare skin manifestations observed in COVID-19 patients include a multisystem inflammatory syndrome in children, anagen effluvium, sebopsoriasis, painful ulcers on the hard palate and tongue, all fingernails onychopathy, diffuse pruritic pustular eruption, SDRIFE (symmetrical drug-related intertriginous and flexural exanthema)-like erythematous rash, pruriginous and painful subcutaneous nodular lesions, eruptive angiomas and a pseudoherpetic variant of Grover disease [35].

PROGNOSTIC ASPECTS

Several studies evaluated the relationship between cutaneous manifestations and clinical evolution of the cases. COVID-19 patients presenting with chilblain-like rashes are generally young patients with less severe disease whereas those with livedo racemosa, retiform purpura and acral ischemia appear to have a different clinical course and a worse prognosis [7]. In the study by Freeman *et al.* [35], rates of hospital admission across the group of patients with pernio-like lesions, erythematous rashes and retiform purpora were 16, 33 and 100%, respectively. Moreover, although maculopapular rashes were associated with an overall mortality rate of 2% [12▪▪], patients with retiform purpura developed

ARDS in 10% of the cases. In the same study, mortality rate was approximately 10% when a necrotic lesion was observed[12▪▪].

OTHER DERMATOLOGICAL MANIFESTATIONS

When considering SARS-CoV-2-positive patients with skin manifestations, possible drug-related reactions should be also considered in differential diagnosis. Adverse events could be immediate or delayed reactions with different immune cells activations, IgE releasing, mast cell activation and eosinophilia [67]. Hypersensitivity reactions have different severity aspects: DRESS (drug reaction with eosinophilia and systemic symptoms) is the most severe manifestation with systemic involvement, liver abnormalities, lymph node enlargement, facial swelling [68]. In addition to the previously discussed hydroxychloroquine, corticosteroids or tocilizumab may both be associated with cutaneous manifestations in COVID-19 patients, including acneiform rash, telangiectasias, petechiae and ecchymoses, erythroderma, or leukocytoclastic vasculitis [63,69–71].

Lastly, although hand hygiene-related dermatitis generally represents an issue among healthcare workers [72], overzealous hand hygiene may cause hand eczema in the general population as well [73]. The frequent usage of emollients, washing with lukewarm water and usage of alcohol-based cleansers when hands are not visibly dirty may reduce the incidence of the disease [74].

CONCLUSION

A significant proportion of patients with COVID-19 display a range of skin manifestations, whose heterogeneity may purportedly represent the diversity in immune response generated to COVID-19. In this sense, skin involvement during COVID-19 may be the results of direct viral damage but other pathogenetic mechanisms including a reactivation of other viruses (e.g. herpes virus in patients with vesicular rash) or a hypersensitivity reaction to the drugs (e.g. hydroxychloroquine) have also to be considered. An in-depth knowledge of skin manifestations in COVID-19 presented in this review as well as their proper recognition may help to timely diagnose, adequately treat and accurate prognose patients with COVID-19.

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Conflicts of interest

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