

Mucocutaneous lesions associated with SARS-CoV-2 infection (Review)

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Abstract. The ongoing COVID-19 pandemic, declared by the World Health Organisation in March 2020, with the emergence of new, possibly more contagious and more virulent strains, remains a research subject, with the complex systemic involvement better described and understood, but also with a variety of skin and mucosal lesions described in the literature. Mucocutaneous lesions associated with SARS-CoV-2 infection are still under investigation, due to their polymorphic clinical aspect and incompletely understood pathogenic mechanism. The cutaneous inflammatory, exanthematous and purpuric rashes, erythematopurpuric enanths, oral ulcers, lichenoid oral lesions, conjunctivitis, conjunctival pseudomembranes, or corneal lesions have been described in patients with COVID-19. Several classifications have been proposed based on the clinical pattern, histological findings, and possible pathogenic mechanisms. The pathogenic mechanism, the diagnostic criteria, the prognostic importance of these

lesions are still being debated. The diverse clinical aspects of dermatological manifestations render the diagnosis difficult. However, several clinical patterns strongly associated with COVID-19, such as chilblains, papulovesicular exanths, and febrile rash require increased awareness and changes to the investigation protocols for these conditions, to include testing for SARS-CoV-2. In the present review, the mucocutaneous findings associated with the novel coronavirus infection, reported thus far in the literature, was provided.

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1. Introduction

Despite the research data currently provided, cutaneous and mucosal manifestations of SARS-CoV-2 infection remain poorly known, particularly their prevalence, their morphological characteristics, the pathogenic substrate, as well as their diagnostic and prognostic significance. The ongoing pandemic, as well as the emergence of new viral strains, possibly more contagious and responsible for more severe disease (1), even with the development of several promising vaccines, that, however, have lower efficacy in a large group of individuals suffering from metabolic disorders, autoimmune diseases or with iatrogenic immune suppression (2), make it

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imperative to understand the complex clinical manifestations of COVID-19, including the signs and symptoms on the skin and mucous membranes. Case reports refer to a variety of morphological aspects that are either virus-induced or associated with antiviral therapy or secondary to the circumstances of the pandemic such as stress (herpes simplex, herpes zoster and alopecia areata) and environmental factors related to the use of antiseptics and disinfectants (contact dermatitis or urticaria) (3-8). According to a French study (conducted by Raymond-Poincaré University Hospital, Garches, France), which involved ~40 patients confirmed positive for COVID-19, the most common mucocutaneous manifestations were: macular exanthema (32 patients; trunk and head and neck were the areas preferentially involved, hand and feet were spared), face edema (13 patients), oral lichenoid reaction (13 patients), enanthema (11 patients), macroglossia (10 patients), cheilitis (5 patients), livedo reticularis (5 patients), urticarial rashes (3 patients), maculopapular exanthema (3 patients), purpura (2 patients), atopic dermatitis (1 patient), herpes (1 patient). All the patients presented extremely itchy lesions (9).

The positive diagnosis of skin and mucosal lesions in patients with COVID-19 is difficult and primarily requires the exclusion of drug-induced dermatoses (10,11) and of other eruptions with similar clinical expression, particularly other viral infections. Cutaneous lesions in patients with SARS-CoV-2 infections are extremely variable in morphological patterns and their importance as a marker for the viral infection and for disease prognosis is still debated (6,12-15). Mucosal lesions are markedly less studied, but there are reports of oral mucous membrane changes and ocular conjunctival or corneal lesions in patients diagnosed with COVID-19, either as solitary findings or in association with cutaneous manifestations, with unclear pathogenic mechanisms, to date (9,16,17).

A classification of the cutaneous lesions associated with SARS-CoV-2 infection based on the clinical aspect, pathogenic hypotheses, histopathological findings, associated disease severity, and prognostic importance, as well as a description of the most commonly encountered oral and ocular mucosal lesions during COVID-19 disease were reported in the present review.

2. Research methods

A literature search was conducted, using electronic databases Key Elsevier, Medscape, PubMed, Google Scholar, for the term 'COVID-19' in combination with 'skin', 'cutaneous manifestations', 'mucosal manifestations', 'rash', 'exanthem', 'enanthem', 'urticarial', 'chilblain', 'livedo', 'ocular mucosa', and 'purpura' to collect reports of skin and mucosal manifestations described in patients with COVID-19. Case reports, case series, and literature review-type articles were included in our research. A brief review was created, based on 63 articles identified in the literature.

3. Prevalence

Literature studies estimate a variable prevalence of the cutaneous and mucosal manifestations related to SARS-CoV-2 infection, between 0.2% (18), among Chinese patients, 15 out of 78 for Russian patients (3) and 20.4% in a study of 148 Italian patients (5).

4. Pathogenesis

The pathogenic mechanism is unclear. It may include the hyperactive immune response, the complement activation, and the microvascular injury. However, there are currently two proposed hypotheses, which classify the cutaneous manifestations of COVID-19 into two groups: i) manifestations linked to a direct cytopathogenic effect on cells such as keratinocytes, which are involved in numerous other viral infections (urticarial rashes, reactions similar to drug eruptions, varicella-like lesions) (12,19); and ii) manifestations linked to an uncontrolled release of cytokines due to alterations involving specific white blood cells, such as T cells and macrophages. This second group could be divided into two other groups: a) manifestations similar to those in macrophage activation syndrome (acral ischemia, gangrene, retiform purpura, livedo racemosa) and b) cutaneous manifestations observed in young patients and linked to the activation of an early type I interferon (IFN) response (chilblain-like lesions) (20).

This hypothesis may provide a possible explanation of the pathophysiological mechanisms of the skin manifestations of COVID-19 disease.

5. Classification and description of cutaneous, oral, and ocular mucosal lesions

Several classifications have been proposed according to the morphological pattern and histological changes. The clinical patterns described include urticarial rash, confluent erythematous/maculopapular/morbiliform rash, papulosquamous rash, papulovesicular exanthem/varicella-like lesions, chilblains, livedo reticularis/racemosa-like pattern, purpuric 'vasculitic' pattern, vasculitides, livedo, and necrotic lesions (3,13,21-23).

Based on the morphological pattern, pathogenic hypotheses, and histological changes, the classification of skin manifestations was adapted into two main groups: i) inflammatory and exanthematous rashes (urticarial rash, maculopapular rashes, and papulovesicular rashes); and ii) vasculitic/vasculopathic lesions: acral ischemic lesions such as chilblain-like and acral ulcers, reticular purpuric lesions such as retiform purpura, livedo reticularis/livedo racemosa, and purpuric vasculitis, purpuric non-vasculitic lesions such as petechial rash and flexural and periflexural purpuric dermatitis. The lesions on the oral and ocular mucosa associated with SARS-CoV-2 infection are also presented.

i) Inflammatory and exanthematous rashes

a) Urticarial rash. The urticarial rash associated with COVID-19 has been reported in numerous publications. It was first mentioned by Recalcati in 16.7% of the total skin manifestations related to SARS-CoV-2 infection (5). Galván *et al* came to the conclusion that it occurs in 19% of cases, appears simultaneously with the systemic symptoms, lasts ~1 week, and is associated with medium-high severity of the infection. Pruritus may be identified in 92% of cases (21). The International League of Dermatological Societies (ILDS)/American Academy of Dermatology (AAD) registry, including over 1,000 patients reported a median duration of 4 days for urticarial rash (24). Freeman *et al* reported that urticarial lesions could be identified in 16% of the total cutaneous lesions, predominantly involve



Figure 1. Urticarial rash consisting of eritemato-edematous pruritic, evanescent plaques on the trunk.

the trunk and the limbs, sparing the acral sites in most cases (Fig. 1) (24). The proposed pathogenic hypotheses include the unspecific activation of mast cells, direct endothelial damage [angiotensin-converting enzyme 2 (ACE2⁺)], antigen-antibody deposits, complement activation, and kinin pathway activation. Whether the wheals are directly correlated with the novel coronavirus remains unclear, the etiopathogenic substrate being difficult to demonstrate, as urticaria may be drug-induced, particularly by antibiotics (12,24,25). With the use of histopathology, Rodríguez-Jiménez *et al* identified a mild case of vacuolar interface dermatitis accompanied by few necrotic keratinocytes compatible with an erythema multiforme-like pattern (26). Amatore *et al* also reported the presence of lichenoid and vacuolar interface dermatitis, associated with mild spongiosis, dyskeratotic basal keratinocytes and superficial perivascular lymphocytic infiltrate in a patient diagnosed with COVID-19 who presented with erythematous non-pruritic annular plaques and fever (27).

b) Maculo-papular rashes. According to Galván *et al*, maculo-papular rashes are the most common skin manifestations in patients with COVID-19 (47% of the cases) (21). They tend to occur concurrently or immediately following the other symptoms of the disease and are suggested to be associated with severe clinical forms, where the mortality may reach 2%. Pruritus may be present in 56% of cases. The evolution is on average 8.6 days (21). Several subtypes have been described: morbilliform rash, erythema elevatum diutinum-like rash, erythema multiforme-like rash (typical target-like lesions mainly on the extremities, but also on the trunk, possibly induced by the virus), and digitiform papulosquamous rash (9,21,23,28). Morbilliform rash presents



Figure 2. Morbilliform rash consisting of erythematous micro-papules and macules on the trunk.



Figure 3. Erythematous macular rash on the trunk.

with maculo-papules or non-pruritic erythematous plaques, predominantly distributed on the trunk and extremities of the limbs excluding the face and the mucous membranes (Figs. 2 and 3). Onset is frequently following the onset of COVID-19 systemic symptoms. Differential diagnosis includes other viral exanthems and drug-induced cutaneous reactions (21-23,28). Pityriasis rosea, including typical and



Figure 4. Papulo-vesicular rash.

atypical digitiform papulosquamous rash, has been described in association with SARS-CoV-2 infection, presumably as an expression of the immune response of the body to high levels of proinflammatory cytokines (21,28,29). Histopathology of these erythematous eruptions, as described by Gianotti *et al*, revealed vascular damage in all the 3 cases examined (30). Reymundo *et al* observed a mild superficial perivascular lymphocytic infiltrate on the histology of 4 patients (31). By contrast, Herrero-Moyano *et al* observed neutrophilic infiltrate in 8 patients with late maculopapular eruptions. Collectively, the histopathology reveals changes similar to other viral rashes (32).

c) Papulovesicular exanthem/varicella-like lesions. Marzano *et al* revealed that the papulovesicular exanthems have a 9% prevalence, the median age is 60 years, but children may also be affected (33). In an unpublished study conducted in eight Italian dermatology units, skin lesions were reported to appear in most cases 3 days following the systemic symptoms and to disappear after 8 days, without scarring (13). The clinical aspect consists of a vesicular eruption similar to varicella (Fig. 4), or miliaria rubra-like disseminated lesions, located mainly on the torso (13,33). Tammaro *et al* presented data from their combined experience in Rome (Italy) and Barcelona (Spain), and described similar lesions to ones identified in infections caused by members of the *Herpesviridae* family (34). Differential diagnosis must include herpetic infections and Grover's Disease (32). As a pathogenic hypothesis, direct viral damage to basal keratinocytes may be considered (28,29,33,34). According to Mahé *et al*, histologically, these exanthems reveal acantholysis, intraepidermal vesicles with suprabasal clefts, prominent, 'pomegranate-like' dyskeratosis and suspected viral inclusions in multinucleated cells (35). Fernandez-Nieto *et al* identified another case of papulovesicular eruption which revealed extensive epidermal necrosis with acantholysis and swelling of keratinocytes, balloon degeneration of keratinocytes, and signs of endothelitis in the dermal vessels (36).

ii) Vasculitic/vasculopathic lesions associated with SARS-CoV-2. The current hypotheses consider that the vasculitic/vasculopathic manifestations could be the result of small vessel occlusion, or it could be a neurogenic, microthrombotic, immune complex-mediated mechanism. A direct correlation with the SARS-CoV-2 virus has yet to be demonstrated (37,38).



Figure 5. Chilblain-like lesions on the toes.

a) Ischemic acral lesions. Ischemic acral lesions were described in patients with COVID-19, presenting two types of clinical manifestations: chilblain-like/perniosis and acral ulcers. Chilblain-like lesions are painful cyanotic, red-purple macular or papular lesions, with acral disposition, particularly in the lower limbs (toes, but also plantar and calcaneal), accompanied by edema (Fig. 5) (21). These lesions occur mainly in children with asymptomatic clinical forms, in 19-40% of adults with less severe disease (16% hospitalized) and in females (68% of cases), at younger ages (31.7 years on average). They appear later in the evolution of the COVID-19 disease, without cold exposure or other predisposing substrates, on average after the 9th day, but in certain cases, even following the recovery period (3,7,11,19,20). The evolution is towards resolution in 2-8 weeks, with a duration of symptoms between 10 and 133 days, according to the ILDS/AAD registry (24). In patients with critical COVID-19 disease and disseminated intravascular coagulation severe manifestations with cyanosis of the toes, bullous lesions, and dry gangrene have been described (22,23). The causal correlation between chilblain-like lesions and SARS-CoV-2 infection is still debated. French researchers did not identify chilblains predictive for COVID-19, as they investigated 40 patients suffering from chilblains, with the nasopharyngeal test (PCR) negative for all of these patients and positive serology in only one-third of them (39,40). However, the increased occurrence of chilblain-like lesions during the COVID-19 pandemic, particularly in young patients with no history of predisposing factors, such as exposure to cold, as well as pathological reports of positive immunohistochemistry for SARS-CoV-2 from skin biopsies are arguments in favor

of a COVID-19-associated type of chilblain (10,41). The pathogenesis of SARS-CoV-2-associated chilblain involves vasospasm and microthrombosis through an increase in the vasoconstricting, prothrombotic and inflammatory pathway of angiotensin 2 induced by the viral cell infection, as well as acquired coagulopathy or endothelial cytotoxicity mediated by CD8⁺ T lymphocytes and robust interferon I (IFN-I) response (20,22,37,41). Histological examination revealed lymphoid-lymphoplasmacytic infiltrate in the dermis possibly extending to the hypodermis and signs of endothelial activation or plump endothelial cells in the venules surrounded by infiltrate (12,42).

An acral ulcer occurs in critically ill patients with COVID-19 with multiorgan involvement and manifests with purplish induration, livedoid plaques, bedsore. The pathogenic mechanism hypothesis focuses on the systemic coagulopathy leading to cutaneous ischemia (22).

b) Reticular purpuric lesions. Reticular purpuric lesions include retiform purpura, livedo reticularis and livedo racemosa. Retiform purpura is a severe manifestation that occurred in 82% of the hospitalized patients with acute respiratory distress syndrome. Its manifestations may include widespread purpura, hemorrhagic bullae, microthrombosis, progressive thrombocytopenia, with or without livedo racemosa (22).

Livedo reticularis/racemosa pattern. Livedo describes a condition of slow blood flow and blue cutaneous discoloration, which has been divided into 2 groups: livedo reticularis, generally associated with cold-induced cutaneous vasoconstriction and livedo racemosa, more frequently associated with focal impairment of blood flow such as Sneddon's syndrome. These lesions are described to appear any time during SARS-CoV-2 infection, mostly in older patients, localized on the limbs (13,21,22). Livedo reticularis-like patterns are frequently mild, transient, unilateral, or bilateral and not associated with thromboembolic complications (43). On the contrary, livedo racemosa-like patterns have often been described in patients with severe coagulopathy (13,21). Regarding the histopathology, Magro *et al* described pauci-inflammatory microthrombotic vasculopathy observed in three patients. They also demonstrated that in the racemosa-like pattern, in patients with a severe infection of COVID-19, the vascular thrombosis was associated with a minimal interferon response which increased viral replication and complement activation, probably involved in the pathophysiology of its clinical complications (41). Genovese *et al* distinguished the group of livedo reticularis/racemosa-like from the purpuric 'vasculitic' pattern since only the last one is considered the expression of a true vasculitis process (13).

Purpuric 'vasculitic' pattern. An Italian multicentric study revealed that this pattern is likely to be very rare representing 8.2% of skin manifestations (9). Joob and Wiwanitkit described the first purpuric lesion during the COVID-19 pandemic, as a petechial rash. Vasculitic lesions were described to appear more frequently in elderly patients with severe COVID-19, representing the cutaneous manifestations associated with the highest risk of death (44). The clinical appearance is that of



Figure 6. Purpuric flexural dermatitis.

palpable purpura, petechiae, hemorrhagic blisters, ulcers, with distribution on the lower limbs, or with purple and necrotic lesions similar to leukocytoclastic vasculitis. It occurs late during SARS-CoV-2 infection (21,22). The pathogenic mechanism involves a complement-mediated inflammation caused by the immune complexes deposited in small vessels, with tissue destruction, associated with pro-coagulant status. Differential diagnosis includes drug-induced vasculitis (20,22). A severe clinical form of vasculitis has been described, involving multisystem inflammatory syndrome in children who develop an exaggerated immune response to SARS-CoV-2 virus, with clinical manifestations similar to Kawasaki disease [acute vasculitis affecting children under 5 years of age and may lead to coronary aneurysms in 25% of untreated cases, triggered by an external factor, infectious agent, in individuals with genetic susceptibility (CASP3, HLA II, BLK, CD40)] (45-47). The mechanism of association of Kawasaki disease with viral infection is incompletely elucidated, but it is assumed that cytokines (IL-1, IL-6, IL-18) released by infected cells induce endothelial injury with vasculitic manifestations (47).

c) Purpuric non-vasculitic pattern. A petechial rash, probably secondary to thrombocytopenia, has been described, accompanied by macular/maculopapular lesions as a result of a non-vasculitic inflammatory process or as secondary lesions during the evolution of a maculopapular exanthem. Purpuric periflexural and flexural lesions (Fig. 6) have also been reported, with incompletely elucidated pathogenesis. These lesions were considered purpuric non-vasculitic since there was no histological evidence of a vasculitic inflammatory process (21,22). Another dermatologic manifestation described in two patients in association with COVID-19 was the 'red half-moon nail sign', with no associated cutaneous lesions, that appeared between 2 and 14 days since the disease onset and persisted following the remission of respiratory symptoms (48,49).

Oral mucosal lesions in patients with SARS-CoV-2 infection. Changes in oral mucous membranes in the context of SARS-CoV-2 disease have also been reported (16,17). Petechial, macular and maculo-petechial enantheams were described in patients with COVID-19 disease, accompanied by a papulovesicular rash, periflexural purpura, and erythema-multiforme-like rash. These mucosal lesions occurring concurrently with a skin rash are indicative of a viral etiology, rendering the examination of the oral mucosa an important step in differentiating between drug-induced

exanthems and viral-induced skin rashes in the context of the SARS-CoV-2 pandemic (16). Lingual pain was described in patients with COVID-19, possibly due to the higher expression of ACE2 receptor in the epithelial cells of the tongue (17). Oral ulcers, similar to recurrent herpes simplex or recurrent aphthous stomatitis have been reported by several authors. Pathogenic hypotheses focus on vascular and arterial thrombosis in small and medium-sized vessels (16,17). Lichen-planus-like lesions have been reported in patients that had been diagnosed with COVID-19 in the previous 12 months (16,17). In a Spanish study, 45.7% of 666 patients presented mucocutaneous lesions. On the oral mucosa, transient lingual papillitis was identified in 11.5% of cases, recurrent aphthous stomatitis in 6.9% of cases, glossitis with lateral indentations in 6.6% of cases, and depapilating glossitis in 3.9% of cases (16). The pathogenic mechanism for these manifestations is not yet fully understood.

Ocular mucosa lesions in patients with SARS-CoV-2 infection.

The conjunctiva is considered to be an important part of the eye mucosa. It has a consistent barrier role against environmental and infectious agents due to numerous immunologic features common to other mucosal tissues (CD4⁺, CD8⁺ T cells, B cells, mast cells, dendritic cells, and Langerhans cells) (50,51). The confirmation of both ACE2 (as the key entry receptor) and cellular serine protease TMPRSS2 expression on the ocular surface cells (52) makes the conjunctiva vulnerable for SARS-CoV-2 infection. In addition, the wide immunohistochemical detection of CD147 (promoter of viral invasion into the host cells), in different eye structures explains the viral propagation and enables ocular surface cells for further person-to-person transmission. The incidence of conjunctivitis in COVID-19 patients largely varies from 0.8% to 4.8% (18,53). A higher incidence (~3%) has been noted in severe COVID-19 cases as compared with only 0.7% in mild to moderate disease (54). The conjunctival signs, mostly bilateral, usually include mild to moderate hyperemia, follicular changes, chemosis, and discharge. A limited number of severe cases develop conjunctival pseudo-membranes or corneal lesions (epithelial defects or subepithelial infiltrates) (55-57). The timing of conjunctivitis largely varies, certain patients reporting conjunctivitis-related symptoms (foreign body sensation, itching, and occasionally photophobia) before respiratory symptoms or fever. The possibility of contracting the SARS-CoV-2 infection via the eye is, at least in theory, plausible as the nasolacrimal duct may transport viral particles from the ocular surface to highly susceptible nasal epithelial cells from the inferior meatus (58). Other intriguing observations are that the detection of SARS-CoV-2 RNA in tears is not always associated with ocular manifestations as not every COVID-19 patient with conjunctivitis has a positive tear sample (59,60).

6. Discussion and conclusions

Although millions of cases have been registered, no pathognomonic dermatological signs and symptoms for the disease have been identified yet. The polymorphic skin and mucosal lesions associated with SARS-CoV-2 infection are not an argument for the viral etiology, as usually, a certain virus is responsible for a single type of dermatologic manifestation. However, the increased incidence of the aforementioned clinical patterns

of dermatologic conditions during the pandemic, suggests the association with the SARS-CoV-2 virus. The diverse clinical aspects may be explained by pathogenic differences between distinct strains of the virus, differences related to the host reactivity, and the possibility of co-infections. In contrast, skin and mucosal manifestations during COVID-19 may not only be related to the virus itself, but also to the viral-induced vasculitis and thrombotic vasculopathy, or they may be due to adverse reactions to the prescribed drugs (6-8,61). The most common side effects associated with several of the often-prescribed drugs for COVID-19 infection (antimalarials) were maculopapular exanthematous reactions, urticaria, and psoriasis exacerbation. Oral antiretroviral combination lopinavir/ritonavir may be responsible for Stevens-Johnson syndrome (8). Temporal association between urticarial lesions and maculopapular eruptions with SARS-CoV-2 infection, when they appear concurrently as the systemic symptoms may be indicative of a viral etiology, rather than a drug-induced one (8). It is currently considered that two types of skin manifestations may be characteristic of the COVID-19 disease chilblain-like lesions and papulovesicular lesions. Therefore RT-PCR for SARS-CoV-2 (if the onset is less than 4 weeks previous) or serological testing (IgM, IgG) for a potential SARS-CoV-2 infection should be added to the investigation protocol in patients without known risk factors who develop pernio-like lesions or in patients with papulovesicular rashes. Cases of COVID-19 with a clinical picture consisting of an infectious rash alone have been reported, making it imperative to investigate a febrile rash for the novel coronavirus as a possible cause (30,61).

The description of the mucocutaneous manifestations associated with COVID-19 reviewed in this article may be helpful in the early recognition of cutaneous signs that are associated with severe complications (such as livedoid, necrotic or maculopapular lesions) and to establish prompt management essential in improving patients prognosis. Patients with autoimmune and chronic inflammatory disorders, such as psoriasis, atopic dermatitis, lupus, scleroderma, and hidradenitis suppurativa may require special care and adjustment of their immune-suppressive therapy protocol in order to maximize the chances for an effective response to anti-Covid-19 vaccines (2).

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Authors' contributions

MPT and DEB contributed to the study design, participated in the entire review process, and prepared the manuscript. IME and CIB contributed to collecting the relevant literature,

data analysis, and critical interpretation. MSC, MG, and DCB conceived the review and modified the manuscript. ACP, AD and ACN ensured that all questions related to the accuracy or integrity of the work are appropriately investigated and resolved. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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